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METASTASIS

T-ALL order

Children and adolescents diagnosed with T cell acute lymphoblastic leukaemia (T-ALL) are often treated with cranial radiotherapy and chemotherapy injected into the cerebrospinal fluid to reduce the risk of central nervous system (CNS) relapse. Although this increases long-term survival, the side effects can be considerable. Iannis Aifantis and colleagues have identified a chemokine receptor, CCR7, as being crucial for CNS infiltration, paving the way for reducing the toxicity of treatments used to prevent CNS relapse.

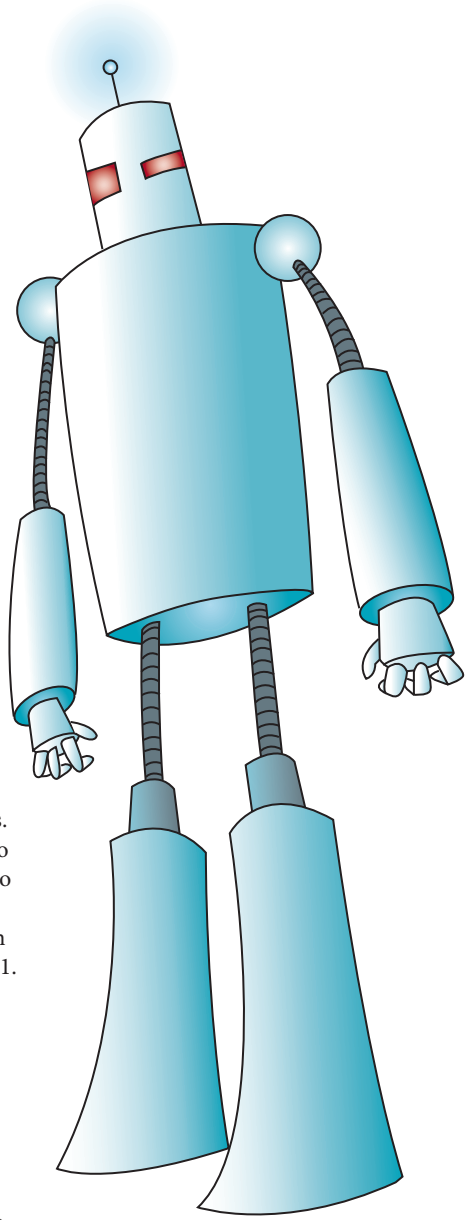
Given that activation of the NOTCH1 pathway occurs in more than 80% of patients with T-ALL, the authors investigated whether the deregulation of this pathway influences CNS infiltration. They reasoned that T-ALL cells able to enter the CNS would need to adhere to their new microenvironment, so they looked for adhesion regulators with increased expression in haematopoietic progenitors expressing the active intracellular fragment of NOTCH1 (NOTCH1-IC). Genome-wide expression studies indicated that *Ccr7* was a potential candidate. T-ALL cell lines with activated NOTCH1 and peripheral blood samples from patients with T-ALL showed that CCR7 expression was strongly associated with NOTCH1 activation. Suppression of NOTCH1 activity using a γ-secretase inhibitor that prevents cleavage and activation of NOTCH1 reduced the expression levels of *CCR7* mRNA.

In vivo, the authors found that syngeneic mice transplanted with *Ccr7*-wild-type or -null haematopoietic progenitors expressing NOTCH1-IC had different rates of disease progression. Mice with *Ccr7*-null cells had a prolonged survival rate compared with their *Ccr7*-expressing counterparts and although T-ALL cells were evident in lymphoid organs in both mouse models, CNS infiltration was significantly reduced in mice with *Ccr7*-null leukaemic cells. Interestingly, deletion of *Ccr7* in two mouse models of B cell ALL failed to inhibit CNS infiltration, indicating that CCR7 has a specific function in T-ALL cells with activated NOTCH1.

CCR7 is bound by CCL21 and CCL19, so are both ligands important for CNS infiltration? Immunohistochemical analyses indicated that only CCL19 was expressed in brain tissue samples taken from mice with T-ALL. Moreover, CNS infiltration in *plt* mice, which naturally lack expression of both CCL21 and CCL19, was significantly reduced compared with wild-type mice. Therefore, the CCR7 receptor–ligand pathway is necessary and sufficient for CNS infiltration of T-ALL cells; however, other adhesion molecules are also likely to be important.

Nicola McCarthy

> “…the CCR7 receptor–ligand pathway is necessary and sufficient for CNS infiltration of T-ALL cells…”



ORIGINAL RESEARCH PAPER Buonamici, S. *et al.* CCR7 signalling as an essential regulator of CNS infiltration in T-cell leukaemia. *Nature* **459**, 1000–1004 (2009)