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LEUKAEMIA

Competition can be a good thing

> cell competition can act to eliminate older progenitors in the thymus and thereby suppress leukaemogenesis

The phenomenon of cell competition between genetically distinct cells with varying degrees of fitness was first identified in *Drosophila* and has been proposed to occur in tumour development and progression. Cell competition might also occur between genetically identical cells, as a mechanism of ensuring normal cell turnover in a tissue, thereby preventing the accumulation of mutations. This could also promote tumour suppression, but direct evidence of such 'natural' cell competition is limited. Hans-Reimer Rodewald and colleagues have found that cell competition occurs in the thymus and that mice lacking such competition develop T cell acute lymphoblastic leukaemia (T-ALL).

The thymus is the site of T cell maturation. T cell progenitors normally migrate from the bone marrow to the thymus; however, when this migration is disrupted, cells within the thymus can maintain T cell development. To model loss of competition between these two sources of T cell progenitors, the authors used mice that lacked recombination activating gene 2 (*Rag2*), interleukin-2 receptor, γ-chain (*Il2rg*) and *Kit* (*Rag2*$^{-/-}$*Il2rg*$^{-/-}$*Kit*$^{W/Wv}$ mice; which do not produce T cell progenitors), into which thymi from wild-type mice were transplanted. T cell development still occurred in the thymi of these mice, despite the loss of bone marrow-derived progenitors. Interestingly, 64% ($n = 25$) of these mice also developed a population of cells that had characteristics of T-ALL.

T-ALL lesions that arose from the transplant of wild-type thymi grafted into *Rag2*$^{-/-}$*Il2rg*$^{-/-}$*Kit*$^{W/Wv}$ mice frequently carried mutations in *Notch1* that are common in human T-ALL. Global gene expression profiling was used to compare T-ALL cells (which are considered to be developmentally 'frozen') with normal cells at different stages of T cell development. This indicated that T-ALL cells that arise under conditions in which bone marrow-derived progenitors are lacking are most similar to cells that are midway along the pathway of T cell development (those of the developmental stages triple-negative 3 (TN3), TN4 or immature CD8 single-positive (ISP)), suggesting that progenitors at these stages undergo malignant transformation and are the cellular origin of the T-ALL. Furthermore, comparison of gene expression data to human leukaemias revealed a correlation between T-ALL derived from this mouse model and human T-ALL, but not human B-ALL, and crucial oncogenes in human T-ALL (such as *TAL1* and LIM domain only 2 (*LMO2*)) were also upregulated in mouse T-ALL.

To look further at the process of cell competition in the thymus, the authors analysed cell turnover in wild-type thymi that were transplanted into either wild-type (competitive) or *Rag2*$^{-/-}$*Il2rg*$^{-/-}$*Kit*$^{W/Wv}$ (non-competitive) mice. Progenitors persisted for much longer in non-competitive mice than in competitive mice; as the loss of one cell population was differentially affected by the presence or absence of another population, this suggests that competition can regulate progenitor turnover in this system. 'Old' thymus-derived progenitors that were subject to competition by 'young' bone marrow-derived progenitors had notable differences in gene expression compared to old cells that were not subject to competition. Interestingly, old thymus-derived progenitors that had been exposed to competition had upregulation of high-mobility group A1 (*Hmga1*), which is typically expressed in both stem cells and several cancers, including T-ALL.

This study provides compelling evidence that cell competition can act to eliminate older progenitors in the thymus and thereby suppress leukaemogenesis. Further understanding of the molecular mechanisms behind this phenomenon in the thymus and determining whether cell competition has a similar role in other tissue types will be interesting future directions.

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