The importance of apoptosis as a tumour suppressive mechanism is well documented, especially in the haematopoietic system, but which components of the apoptotic pathway, through either their gain or their loss of function, can promote tumour development is still being established. A recent paper in *Genes and Development* indicates that reduced expression of the pro-apoptotic protein ARTS, which is an inhibitor of X-linked inhibitor of apoptosis (XIAP), can promote the development of leukaemia and lymphoma by enabling the aberrant survival of haematopoietic stem and progenitor cells.

Expression of ARTS (encoded by *SEPT4*) is reduced in human leukaemias, so Maria Garcia-Fernandez and colleagues generated Sept4-knockout mice to examine the effect of loss of ARTS on tumour development. Sept4 encodes several splice variants that function as septins, which are essential for cytokinesis, but ARTS is the only splice variant known to inhibit XIAP and it is expressed in cells undergoing apoptosis. One-third of Sept4−/− mice and 10% of Sept4+/− mice spontaneously developed leukaemia and lymphoma between 11 months and 15 months of age. Examination of the haematopoietic compartment in Sept4-null mice indicated no increase in the rate of cell proliferation, but instead showed an increase in the number of B-lineage progenitor cells, immature B cells and haematopoietic stem cells (the Lin−, Sca−, KIT+ (LSK) population). Bone marrow repopulating assays in irradiated syngeneic mice also indicated an increase in the number of LSK cells in Sept4-null mice. *In vitro* colony formation assays using irradiated populations of progenitor and LSK cells from the Sept4-null mice showed that these cells were more resistant to cell death and had increased levels of XIAP expression than cells from wild-type mice. The authors examined the expression levels of the Sept4 splice variants in LSK cells and B cell progenitors from wild-type mice and found that Arts mRNA expression was increased in these cells compared with the expression of other splice variants.

These findings suggest that the loss of ARTS expression increases the number of stem and progenitor cells because XIAP function is not inhibited in these cells, making them more resistant to cell death. Consistent with this, the rate and number of Sept4−/− mice and Sept4+/− mice developing lymphoma was significantly increased when these mice were crossed with *Eμ-Myc* lymphoma-prone mice. Overexpression of MYC induces apoptosis, indicating that the loss of ARTS can counteract this, which is similar to the overexpression of the anti-apoptotic protein BCL-2. This effect was reduced in Sept4−/−; *Xiap−/−*; *Eμ-Myc* mice. Therefore, reduced expression of ARTS expands the population of stem and progenitor cells and so increases the likelihood that one or more of these cells will attain further mutations that enable tumour development.

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**ORIGINAL RESEARCH PAPER**