The origin of epithelial neoplasms after allogeneic stem cell transplantation

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We read with great interest the article: *The origin of epithelial neoplasms after allogeneic stem cell transplantation*, Haematologica 2006; 91:283-284 by Johan H. J. M. van Krieken and colleagues in which the authors studied patients who developed breast neoplasias after stem cell transplants from donors of the opposite sex. None of these neoplasms appeared to arise from donor cells. This is a negative study, and as it is hard to prove a negative, we would suggest keeping an open mind regarding the possibility that stem cells may participate in the formation of epithelial malignancies for the following reasons.

First, the authors concluded that n*one of the non-haematologic malignancies was of donor origins* based on the absence of the Y-chromosome. Loss of the Y-chromosome is a well described phenomenon in male breast cancer. [1-3] While it is unlikely that all of the tumors sustained Y-chromosome loss, it is possible that one or more of the tumors arose from donated male stem cells that then lost a Y-chromosome. In addition, the authors did not specified whether the in-situ hybridization was done on sequential sections spanning at least [2] cells in width. The possibility of not detecting the Y-chromosome using in-situ hybridization on non-sequential sections and spanning less than one cells was described previously.

Second and more importantly, the preconditioning treatment that these patients received is very unlikely to ablate every stem cell in the body and in particular the niche protected, tissue localized stem cells (as opposed to the rodent model of gastric cancer in which much higher relative doses of radiation are given). [4] These neoplasms could have arisen from persisting residual recipient stem cells.

Third, even if stem cells are not the cell of origin of epithelial cancers, they may still participate in the ongoing development of the disease (propagating cells), perhaps by fusion. In the fourth paragraph, the authors state that they noted *donor inflammatory cells based on morphology*. Morphologically, stem cells and lymphocytes (in particular early lymphocytes) are very similar. Is it possible that some of these 'inflammatory' cells are instead stem cells that will participate in tumor progression?

Fourth, the interval from the bone marrow transplant to the appearance of these cancers is of utmost importance. Patients one and two (the only patients with invasive breast cancer) developed cancer at 1.5 and 5 years after transplant. It is entirely likely that these cancers had been initiated well before the stem cell transplant was performed, and therefore, if derived from stem cells, would have been from recipient cells. The only patient with a sufficiently long interval after BMT (10 years) to make it likely that if stem cells were the cell of origin, then the tumor would be expected to be derived from the donor did not have an invasive cancer but LCIS. If one follows the Gompertzian model of human breast cancer growth, an average of 8 years of growth from one cell to clinically detectable tumors are required.[5]

Finally, the authors have incompletely cited the literature. Two papers from a single institution have provided evidence that epithelial malignancies arising after bone marrow transplants may arise from donor cells. In the first report, BMT donor DNA was found in malignant tissue from a child who after allogeneic liver and bone marrow transplants from a donor of the same sex developed metastatic renal cell carcinoma. 6 In the second report, a woman, who had received a BMT from her son, developed a renal cell carcinoma which by FISH contained Y-chromosomes suggesting donor origin, most likely from donated stem cells.[7] Unfortunately, the specimens were not stained for CD-45 leaving open the possibility that the cells containing Y-chromosomes were actually lymphocytes.

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