The pathway to cancer

Editorial

For some time, we have tried to define the steps involved by which normal cells become cancer cells. We have attempted to answer this question starting with a nontransformed (anchorage dependent, nontumorigenic) cloned cell line. This in itself may, in fact, be a problem. Clearly one of the first steps on the pathway to cancer is the acquisition of immortality. If cancers arise that are not immortal, then in vitro studies that suggest that suggest that these cancers would never reach a cell mass that would be identifiable.4,5 Although we believe that immortality may be an early step in the progression to cancer, we also realize that experimentally it may be a step that is difficult to characterize in vitro. It is relatively easy to isolate permanent cell lines from primary cell cultures. The problem is once you establish a permanent cell line from primary cells the progenitor cell that was the origin of permanent cell line is no longer available. Comparing cells of a primary cell cultures to cells of a permanent cell line is not an ideal model for the analysis of the steps involved in the pathway to cancer. Given this short coming, we nonetheless believe that we can identify one of the earliest steps in the pathway to cancer: transformation. There is considerable evidence that cells that are dependent on attachment to a substrate (anchorage dependent) do not grow as tumors even in immune suppressed animals. There is also considerable evidence that cancers derived from tissue that would normally require a substrate for growth in vitro, show anchorage independent in vitro, that is, they are capable of growth in agarose or methylcellulose.6,7 Selection for cells that grow anchorage independent in vitro results in cells that are capable of growth in at least immune suppressed animals. Further selection of cells the grow as tumors results in cells that grow anchorage independent in vitro. The fact that cells that express the selected marker also express the unselected marker is the strongest evidence that tumorigenicity and anchorage independence are, in fact, coordinately controlled by the same gene(s).

As a starting point a cloned anchorage dependent nontumorigenic Balb/c mouse fibroblast cell line (normal, N-cell) was exposed to methylcholanthrene. After exposure to methylcholanthrene cells capable of growth in agarose (anchorage independent) were selected and cloned. The tumorigenic potential of the anchorage independent cell lines was determined in normal mice and adult thymectomized, lethally irradiated (750 rads) and restored with syngeneic fetal liver (ATXFL) Balb/c mice. Those anchorage independent cell lines that only grew as tumors in ATXFL mice were designated intermediate, (I-cells) cell lines. I-cells were injected into normal mice in order to select for cells capable of growth not only in ATXFL mice but also in normal mice. The cells that grew as tumors in normal mice were isolated and cloned in vitro. These cell line were designated cancer, (C-cells) cell lines. This established lineages of sequentially derived cell lines; N→I→C (normal cells → intermediate cells→cancer cells).8,9 Several facts are important to understanding tumor surveillance in this system. I-cells only grow as tumors in immune depressed (ATXFL) mice. Normal mice have normal levels of natural cytotoxic (NC) cell activity. ATXFL mice have greatly reduced levels of NC cell activity. I-cells are sensitive to mouse NC cell mediated lysis in vitro. The fact that I-cells grow as tumors in ATXFL mice, but not in normal mice is consistent with the tumor surveillance of I-cells by NC activity. In support of this is the fact that C-cells are resistant to mouse NC mediated lysis in vitro. It thus appears that when N-cells are transformed to tumorigenic I-cells these cells are eliminated in normal mice by NC cell activity. If they escape tumor surveillance and become resistant to NC mediated lysis they are able to grow as tumors in normal mice, i.e., C-cells.

Using these same sequentially derived cell lines; N→I→C, we have shown that humans also express NC cell activity and surprisingly human NC activity is capable of lysing mouse I-cells, but not N-cell or C-cells, in vitro.10 This suggests that human may also express a tumor surveillance mechanism based on NC cell activity. Two things limit an analysis of a human tumor surveillance mechanism by NC cells. First, by definition tumor that arise in otherwise normal human must have escaped tumor surveillance to grow as tumors, that is they would be C-cells. Second, although there is some evidence that humans who are immune compromised have an increased risk of cancer,11-13 we know of no cases of humans who have reduced levels of NC activity. If such human could be identified their tumor might be I-cells. The fact that human NC cells are capable of recognizing and lysing mouse I-cells in vitro may provide a system to further explore the potential of an NC mediated surveillance mechanism in humans.

Acknowledgments

None

Conflicts of interest

The author declares there are no conflicts of interest.

References


