Cancer stem cells generated by cancer outgrowth

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Scientists have discovered that growing mouse skin cells in spheres can lead to generation of cells with properties of cancer stem cells, even without genetic manipulation of stem cell genes. This unexpected finding, published by Cell Press in the April 3rd issue of the journal *Cell Stem Cell*, provides a potential pathway for generation of cancer stem cells from differentiated cells and may even eventually lead to safer strategies for creation of induced pluripotent stem cells for use in regenerative therapies.

"A hallmark of all solid tumors is the outgrowth of cancer cells into three-dimensional structures," explains senior study author, Dr. Douglas C. Dean, from the University of Louisville Health Sciences Center in Louisville, Kentucky. Dr. Dean and colleagues examined whether abnormal cell configurations might trigger reprogramming of differentiated cells into cells that resembled cancer stem cells.

The researchers observed that mutation of all of the retinoblastoma tumor suppressor gene (RB1) family members, known to be critical for regulating cell-contact inhibition and restricting growth of normal cells into three-dimensional tumor-like structures, led to an outgrowth of cells into spheres that triggered generation of cells similar to cancer stem cells. Surprisingly, the cancer stem cell-like cells expressed key genes expressed in embryonic stem cells and gave rise to a variety of differentiated cells.

Interestingly, cells with only one RB1 mutation remained contact

inhibited, but when mechanically scraped off the dish and forced to form spheres, they also exhibited cancer stem-like characteristics. Even cells with intact RB1 genes could be forced to form spheres, suggesting that the reprogramming did not require the loss of RB1. The researchers went on to show that the cancer stem-like cells isolated from the spheres with disrupted RB1 genes formed tumors when injected into mice and differentiated into mature cells in advancing cancers.

These results using cultured cells lead the authors to hypothesize that cancer stem cells may be generated as a direct function of the outgrowth of cells in the animal. "To our knowledge, this is the first example that silenced endogenous embryonic stem cell genes can be spontaneously reactivated in differentiated cells," says Dr. Dean. "We propose that the loss of cell contact inhibition when the RB1 pathway is inhibited leads to outgrowth into sphere-like structures, and these conditions in the advancing cancer trigger reprogramming of differentiated cells to cells with properties of cancer stem cells."

Source: Cell Press (news : web)

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