Stem cell research is currently at the frontier of medical science. Embryonic stem cells, therapeutic cloning, tissue regeneration—research into the vast therapeutic possibilities inherent in understanding and manipulating stem cells is exploding. Amid all this activity, understanding of the role that stem cells play in carcinogenesis has also been increasing.

Stem cells have an extended replicative lifespan, which makes them excellent candidates for the cell of origin of cancer. The standard multi-step somatic mutation theory of carcinogenesis requires that a cell acquire several critical mutations in the cell cycle or proliferation pathways, or both. The extended replicative lifespan of stem cells, or of primitive progenitor cells, would provide the opportunity over the lifespan of an individual for these rare, random mutations to accumulate in a cell.

As reasonable as this argument seems, stem cells as the cell origin of cancer is not currently a favoured model. Although a stem-cell origin of cancer was initially proposed more than thirty years ago, research in this area has been overshadowed by massive amounts of work focussed on elucidating the genetic mechanisms of the underlying somatic mutation theory. The reasons for this focus, as addressed by Sonnenschein and Soto, are complicated and controversial.

Until very recently, a stem- or progenitor-cell origin in carcinogenesis found support only in leukemia research. There, it was first accepted that both hematopoetic stem and progenitor cells could acquire genetic abnormalities that would lead to the uncontrolled replication and dysregulated differentiation that are characteristic of the spectrum of leukemic cancers. The possibility that a similar stem-cell origin of carcinogenesis might apply to solid malignant tumours was not vigorously pursued and has only recently been experimentally addressed.

In 2003, Al-Hajj et al. provided the first evidence for the existence of breast cancer stem cells. They identified a subpopulation of tumour cells that was 10–50 times more tumorigenic in xenografts than were cells from the bulk of the tumour. The cells in this subpopulation were also able to give rise to further tumorigenic cells—and to partially differentiated, non-tumorigenic cells. Continued experimental investigations of these breast cancer stem cells have lent considerable support to the theory of a stem-cell origin in carcinogenesis in solid malignant tumours. Currently, intriguing evidence is also coming from other investigators for the existence of stem-cell involvement in several other solid malignancies, including those of prostate, ovary, lung, and brain.

An unexpected twist to the model of stem-cell carcinogenesis was revealed in a study of gastric cancer, wherein the cell of origin of the cancer was found to be not only a stem cell, but a stem cell derived from bone marrow, not from gastric epithelium!

The foregoing findings, together with data from earlier studies by one of the present authors (RJA), have been incorporated into a revised theory of the stem-cell origin of cancer, in which circulating bone marrow–derived stem cells may become tumorigenic in a variety of chronically inflamed tissue compartments. Future work will reveal if bone marrow–derived stem cells or local-tissue stem cells are indeed the origin for many, or perhaps most, human epithelial cancers.

As the current explosion of interest in stem cells and their therapeutic possibilities continues, the knowledge gained should stimulate further interest in developing the stem-cell theory of carcinogenesis. Whatever the exact involvement of stem cells in the origin of cancers is ultimately found to be, the great hope is that new therapeutic approaches targeting the cancer stem cells within tumours will, in conjunction with current therapies that target the bulk of the tumour, provide oncologists with improved armaments in the war against cancer.

REFERENCES

2. Pardal R, Clarke MF, Morrison SJ. Applying the principles of...

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