IN THE NEWS

Social responsibility

According to Bernard Stewart — co-author of the World Cancer Report released earlier this month by the World Health Organization (WHO) — “Governments, physicians and health educators... could do much more to help people change their behaviour to avoid preventable cancers” (*BBC News*, 3 April 2003).

This report — the first comprehensive global examination of cancer — predicts that global cases could double by the year 2020. Nevertheless, with existing knowledge, Stewart is confident that “...we can prevent a third of cancers, we can probably cure a third of cancers and for the remainder we can certainly do something for quality of life...” (*Washington Post*, 3 April 2003). With world cancer mortality rates twice that of developing countries and because of the unhealthy Western lifestyle, Dr Paul Kleihues — Director of the WHO’s International Agency for Research on Cancer — is not convinced. “I think what we can do is slow down the increase. Anything more is not realistic” (*Startribune.com*, 4 April 2003).

A major concern for experts is the increasing trend towards a Western lifestyle in developing countries. Kleihues predicts cancer rates will soar, as early detection and treatment is not as advanced. Dr Gro Harlem Brundtland — Director-General of WHO — hopes the report will do much to address these issues, saying: “The report provides a basis for public health action and assists us in our goal to reduce the morbidity and mortality from cancer, and to improve the quality of life of cancer patients... everywhere in the world.” (*BBC News*, 3 April 2003).

Emma Croager

BREAST CANCER

An elitist sport

Is tumour formation a ‘first-past-the-post’ situation, in which all cells have an equal ability to become tumorigenic and cells race to see which accumulate the correct set of mutations first, or is it more elitist? Perhaps only a few cells possess this extraordinary ability. Michael Clarke and colleagues, reporting in *Proceedings of the National Academy of Sciences*, have found that a subset of cells that comprise just a small proportion of a tumour are actually able to initiate tumorigenesis.

Human breast cancer cells were isolated from nine patients — one from the primary tumour and the others from metastatic pleural effusions — and were used fresh, from frozen samples, or following passage through mice. These cells were heterogeneous with respect to cell-surface markers, so the authors investigated whether the markers could distinguish between tumorigenic and non-tumorigenic cells. The cells were separated by flow cytometry according to whether they were positive or negative for the adhesion markers CD44 and CD24, and 200,000–800,000 cells were injected into the mammary fat pads of mice. After 12 weeks, tumours had formed at the site of injection in all mice with CD44⁺ and CD24^{-/low} cells, but in no mice with CD44⁻ and CD24⁺ cells (although 2 of 12 mice injected with CD24⁺ cells contained small growths, possibly due to contamination with a different cell type).

Cancer cells were found not to express lineage markers, so the elimination of lineage⁺ cells removed normal human cells such as leukocytes and fibroblasts, leaving only lineage⁻ cancer cells. Of these, 11–35% (depending on tumour type) are CD44⁺CD24^{-/low}. Interestingly, fewer of these cells need to be injected to generate tumours — they seem to have a 10–50-fold enrichment in tumorigenic activity. But can this cell population be further defined in terms of this activity?

The ESA marker has previously been used to distinguish epithelial and mesothelial cells, and the isolation of ESA⁺CD44⁺CD24^{-/low} lineage⁻ cells from three tumours led to further enrichment of tumorigenic ability — as few as 200 cells were able to generate tumours after 4–6 months, compared with the 2,000 CD44⁺CD24^{-/low} lineage⁻ cells or 20,000 unsorted tumour cells that were needed to establish tumours.

The difference in ability was not due to changes in the cell cycle, as the ESA⁺CD44⁺CD24^{-/low} lineage⁻ cells had the same cell-cycle distribution as the other lineage⁻ cells. These cell populations were also morphologically and histologically indistinguishable when assessed before injection, but when the injection sites were examined 6 months after injection, those with CD44⁺CD24^{-/low} lineage⁻ cells contained palpable tumours and malignant cells, and those with CD44⁺CD24⁺ lineage⁻ cells contained no tumours and only normal mouse epithelial cells.

Tumours normally contain a heterogeneous mix of cells, so are the CD44⁺CD24^{-/low} lineage⁻ cells similar to stem cells in their ability to give rise to diverse cell types? Either 200 ESA⁺CD44⁺CD24^{-/low} lineage⁻ cells or 1,000 CD44⁺CD24^{-/low} lineage⁻ cells were injected into mice, and the tumours that formed were analysed by flow cytometry. Both cell types were able to generate heterogeneous expression patterns of the ESA, CD44 and CD24 markers, which resembled the tumours from which they were originally derived. So, the tumorigenic cells were able to generate both tumorigenic CD44⁺CD24^{-/low} lineage⁻ cells and diverse non-tumorigenic cells.

Clarke and colleagues have therefore identified a subpopulation of tumorigenic breast cancer cells that resemble stem cells in their ability to proliferate and give rise to diverse cell types. This discovery is important for both basic and clinical research, as the molecular pathways that are involved in breast cancer development will be easier to characterize and therapeutics could be developed that target proteins specifically expressed by this cell population.

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References and links

ORIGINAL RESEARCH PAPER Al-Hajj, M., Wicha, M. S., Benito-Hernandez, A., Morrison, S. J. & Clarke, M. F. Prospective identification of tumorigenic breast cancer cells. *Proc. Natl Acad. Sci. USA* **100**, 3983–3988 (2003)

FURTHER READING Dick, J. E. Breast cancer stem cells revealed. *Proc. Natl Acad. Sci. USA* **100**, 3547–3549 (2003)

WEB SITE

Michael Clarke's lab:
<http://www.med.umich.edu/cmb/faculty/clarke.htm>