Viewpoint

Introducing the concept of breast cancer stem cells

Alison Waterworth

Molecular Medicine Unit, Clinical Sciences Building, St James’s University Hospital, Leeds, UK

Corresponding author: Alison Waterworth (e-mail: alisonwaterworth@doctors.org.uk)

Published: 20 November 2003

Breast Cancer Res 2004, 6:53-54 (DOI 10.1186/bcr749)
© 2004 BioMed Central Ltd (Print ISSN 1465-5411; Online ISSN 1465-542X)

Introduction

Breast tumours are well known to be composed of phenotypically diverse groups of cells. Which of these cell types contribute to tumour development, however, is not well understood. Two hypotheses exist: either all the cell populations have the capacity to become tumourigenic through mutation accumulation, or this ability is confined to a select ‘elite’ group [1]. In acute myelogenous leukaemia it has been shown that a distinct subset of cells has increased ability to initiate tumourigenesis and may be identified with specific cell surface markers [2,3]. This phenomenon has not been shown in solid tumours until the recent publication by Al-Hajj and colleagues where they describe a method for differentiating ‘tumour-initiating’ or ‘tumourigenic’ breast tumour cells from non-tumourigenic cells [4].

Identification of tumourigenic breast cancer cells

Al-Hajj and colleagues used a xenograft model in which human breast cancer cells were grown in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice. Primary cultures of breast cancer cells were obtained from nine patients (one primary tumour and eight metastatic pleural effusions). These cells were heterogeneous with respect to cell surface markers and were separated by flow cytometry into CD44 and CD24 positive and negative subgroups. 200,000–800,000 cells were injected into the mammary fat pads of mice and after 12 weeks tumours had only formed in the mice injected with CD44+ and CD24–/low cells. Lineage markers are associated with normal cell types (e.g. fibroblasts, leukocytes, endothelial cells and mesothelial cells) and are not expressed by cancer cells. By eliminating Lineage+ cells from the CD44+CD24–/low population as few as 1000 cells consistently formed tumours in the mouse model. Further selection for epithelial-specific antigen (ESA) positive cells enriched the tumour-initiating ability of the CD44+CD24–/low Lineage– cells even further with only 200 cells now producing tumours in the NOD/SCID mice. ESA+CD44+CD24–/low Lineage– cells were therefore identified as the tumourigenic breast cancer cells.

Importantly, the tumours established by the tumourigenic breast cancer cells regained their phenotypic diversity and contained the same heterogeneous expression of CD44, CD24 and ESA as the original donor. On serial transplantation in mice, once again, only the ESA+CD44+CD24–/low cells were able to initiate tumours. In this way, the tumourigenic breast cancer cells were shown to resemble normal stem cells in their ability to self renew, proliferate and differentiate into diverse cell types. This phenomenon may help explain a number of clinical observations including the frequent finding of micrometastases in the bone marrow of breast cancer patients that only rarely give rise to clinically metastatic disease. These micrometastases may be either tumourigenic or non-tumourigenic breast cancer cells and only the tumourigenic population will be able to progress to clinical significance.

Conclusion and future directions

Al-Hajj and colleagues have identified a critical population of cancer cells that drive tumour growth and are hypothesised to be the ‘stem cells’ of breast cancer. This is a significant development and is the first time this phenomenon has been shown in solid tumours. Research directed at these tumourigenic breast cancer cells to identify their unique properties will be crucial to understanding the origin and propagation of breast tumours. Current medical therapies directed at the whole tumour may cause regression of the cancer, but this new research proposes that unless they specifically target these breast cancer-initiating cells they will not eradicate the tumour completely. These findings open an exciting avenue for future research and novel therapeutic strategies.

ESA = epithelial-specific antigen, NOD/SCID mice = nonobese diabetic/severe combined immunodeficient mice.
Competing interests
None declared.

References
1. Reya T, Morrison SJ, Clarke MF, Weissman IL: Stem cells, cancer, and cancer stem cells. Nature 2001, 414:105-111.
2. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M, Paterson B, Caligiuri A, Dick JE: A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 1994, 367:645-648.
3. Bonnet D, Dick JE: Human acute leukemia is organized as a hierarchy, which originates from a primitive hematopoietic cell. Nat Med 1997, 3:730-737.
4. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF: Prospective identification of tumourigenic breast cancer cells. Proc Natl Acad Sci USA 2003, 100:3983-3988.

Note
This article is based on a paper highlighted by Faculty of 1000 (http://www.facultyof1000.com/start.asp), a web-based literature awareness service. Faculty of 1000 evaluations available for articles cited in this report may be viewed at: http://www.breast-cancer-research.com/reports/bcr749.asp

Correspondence
Alison Waterworth, Molecular Medicine Unit, Clinical Sciences Building, St James’s University Hospital, Leeds LS9 7TF, UK. Tel: +44 (0) 113 206 6655; fax: +44 (0) 113 244 4475; e-mail: alisonwaterworth@doctors.org.uk