Viewpoint

Introducing the concept of breast cancer stem cells

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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 $CD44^+CD24^{-/low}$ $Linage^-$ cells even further with only 200 cells now producing tumours in the NOD/SCID mice. $ESA^+CD44^+CD24^{-/low}$ $Linage^-$ 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.

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Note

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