Pathology (February 2010) **42(2)**, pp. 105–112

REVIEW

The elaboration of a critical framework for understanding cancer: the cancer stem cell hypothesis

CHRIS HEMMINGS

ACT Pathology at The Canberra Hospital, Canberra, Australian Capital Territory, and School of Surgery, University of Western Australia, Perth, Western Australia, Australia

Summary

The cancer stem cell hypothesis suggests that malignant tumours may arise from a limited number of specialised cells possessing the key 'stem' properties of self-renewal and the ability to produce differentiated progeny. Such cells purportedly constitute a small fraction of most tumours but have greater potential to produce new tumours than their 'non-stem' counterparts. However, they have proven difficult to identify and characterise in most malignancies. Cancer stem cells are liable to be resistant to most forms of conventional chemotherapy and radiation and so may help to explain tumour recurrence after a seemingly good response to initial therapy.

This review examines the evidence for the existence of such cells, the therapeutic implications of this hypothesis, and problems posed by it, as well as outlining the concept of the stem cell niche and its possible role in tumour development and progression.

Key words: Cancer, stem cell, niche, tumourigenesis, cancer-initiating cells, tumour stroma.

Received 16 August; revised 4 November; accepted 5 November 2009

HISTORICAL PERSPECTIVE

Despite dramatic recent advances in our knowledge of tumour biology, understanding the fundamental origins of cancer remains elusive and its eradication continues to frustrate those involved in the care of cancer patients. Many current treatments can substantially reduce or apparently eliminate a tumour, but the risk of recurrence haunts patients and their doctors alike. Indeed, the ability of a cancer to recur, often at multiple sites, after removal of the primary tumour has been likened to the mythical Hydra, who grew two new heads for every one that was severed by the Greek hero Hercules.[1] Hercules eventually triumphed over his foe when he realised that there was an immortal central head that must be destroyed. Many of the currently available therapies are successful in removing the peripheral heads, but cancer stem cell theory may provide the key to a Herculean triumph.

The idea of a cancer stem cell is not new; whereas Virchow postulated that tumour cells must come from normal cells[2] (i.e., all cells have the ability to give rise to a tumour which then undergoes clonal evolution – an early iteration of the 'stochastic' model of tumourigenesis), his contemporary Julius Cohnheim theorised that tumours are not derived from normal adult tissues, but from 'embryonal cell rests', or residual embryonic cells 'left behind' in the adult. These cells could later become 'activated' to form cancer.[3] More recently this theory has been supported by the discovery of a number of cell signalling pathways shared by embryonic cells and cancer cells. Furthermore, the observation that 'promotion' of carcinoma may eventuate months or years after the initial exposure to a carcinogen ('initiation') implies that the initiating event occurs in a long-lived epithelial stem cell population.[4]

THE CONCEPT OF 'STEM-NESS'

Stem cells comprise zygotic cells, pluripotent embryonic cells and more lineage-restricted, tissue-specific adult stem cells. More clearly defined examples of the latter include glial, skin, skeletal muscle and mammary stem cells. Less well understood adult stem cells in other tissues include those in small and large intestine, liver, pancreas and gonads, whilst those in other organs (such as stomach) remain as yet poorly defined.[5] Nonetheless, several fundamental properties of stem cells have been delineated, chiefly the capacity for (essentially unlimited) self-renewal, the ability to produce differentiated progeny and the capacity for self-preservation (via strategies including activation of anti-apoptotic pathways, increased activity of membrane transporters, and enhanced DNA repair activity).[1]

Adult stem cells normally remain largely quiescent, dividing very slowly and typically undergoing asymmetric replication, producing one identical, quiescent daughter cell with developmental potential identical to that of its parent, and one transit-amplifying or progenitor cell which then goes on to further cell division and differentiation (Fig. 1). Transit-amplifying cells are thought to sequentially lose their capacity for self-renewal as with each cell division they differentiate to generate mature cells of one or more types within the tissue[6] (e.g., in the intestine they may ultimately give rise to neuroendocrine cells, goblet cells, absorptive cells, and so on). Transit-amplifying cells therefore have a limited lifespan, being periodically replaced by the parent stem cell. This stem cell mechanism of maintaining a relatively dormant state theoretically provides protection from mutation, leaving the more genetically risky task of replication to its dispensable offspring. Furthermore, as stem cells are important for tissue growth and repair, they

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: 10.3109/00313020903488773

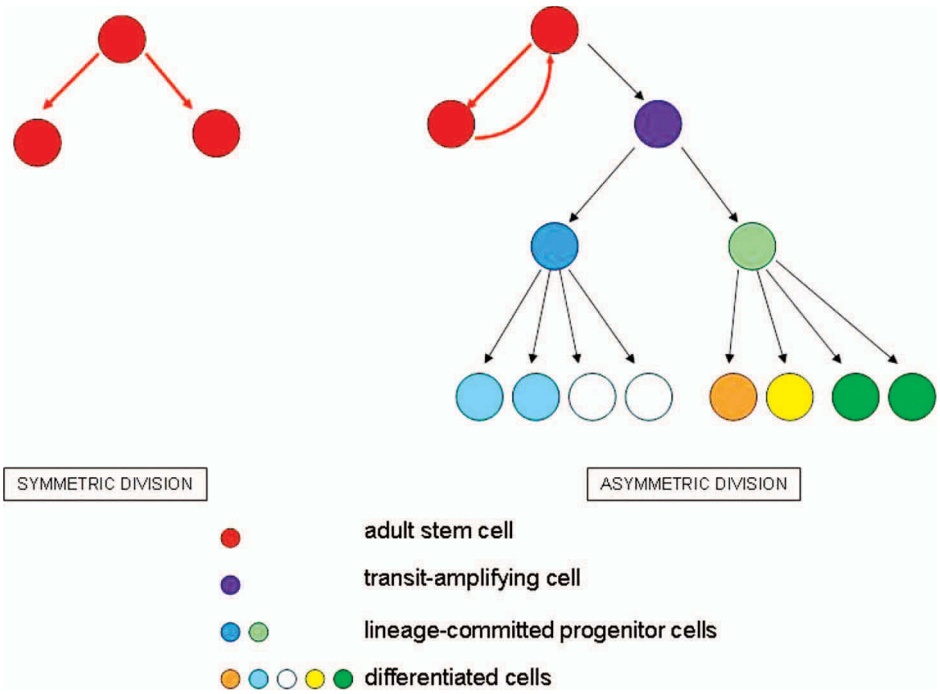

Fig. 1 Whereas symmetric division results in two identical daughter cells, asymmetric division produces an identical daughter (stem) cell and gives rise to more differentiated progeny.

have well developed mechanisms for avoiding apoptosis, and are thereby resistant to radiotherapy[7] and some types of chemotherapy[1,8] (further chemoresistance coming from their slow rate of division, as well as through the expression of drug-resistance transporter proteins). The 'stem cell niche' (described below) is believed to be largely responsible for this slow division, which provides protection from DNA damage or exhaustion, and thereby protects the host from unregulated stem cell growth.[5] Thus changes in the niche may be vitally important in the development of stem cell malignancy.

STEM CELLS IN CANCER

It has been suggested that the capacity of a tumour to grow and propagate depends on a small subset of tumour cells called cancer stem cells or cancer-initiating cells, thought to constitute a small subset of distinct cells (perhaps <1–2% of total tumour cells), having great proliferative potential and the ability to form new tumours, i.e., these cells can both self-renew and produce differentiated progeny,[9] thus meeting two fundamental criteria for definition as a stem cell. It was initially postulated that these putative cancer stem cells must arise either from mutations in adult stem cells in the tissue in question (Fig. 2), or from a more centralised source of stem cells; however, this has subsequently been questioned (discussed below). At any rate, tumour formation has been considered by some to result from disordered stem cell self-renewal.[6]

In many tissues in which malignancies frequently arise (such as colon), mature cells are short-lived, terminally differentiated and post-mitotic, and therefore have limited opportunity to accumulate sufficient mutations to become malignant. So (in keeping with the usual step-wise model of carcinogenesis) in order to give rise to a malignant tumour, a cell would need to be long-lived or 'immortal' – or possess the capacity for self-renewal. Therefore, cells with extended proliferative potential are more likely to generate a tumour; thus, it has been proposed that cancers are caused by transforming mutations occurring in tissue-specific stem cells.[10] As adult stem cells are normally under strict control from intrinsic and extrinsic factors, transition to a cancer-initiating or cancer stem cell would involve loss of this control through both oncogenic alterations in the cell itself (loss of intrinsic control, or cancer initiation), and modification of the surrounding microenvironment (or niche), resulting in a loss of extrinsic control (promotion).[11]

EVIDENCE FOR THE EXISTENCE OF CANCER STEM CELLS

In order to characterise putative cancer stem cells they must be able to be isolated from their surrounding progeny. Their identification may be achieved by the expression of characteristic cell surface markers, their ability to expel certain chemicals (for this purpose, dyes), or by DNA labelling. Expression or down-regulation of various cell-surface proteins has yielded characteristic expression patterns for several tumour types, some of which are described below; however, it is unclear whether isolating cells with those expression patterns will yield a pure culture of cancer stem cells, or simply enrich the population. Furthermore, most of the markers are also expressed on normal stem cells of various types, and on putative cancer stem cells from other tumour types, and the usual problems of non-specific staining, cross-reactivity and false positive results further muddy the waters. An alternative method for detecting a subpopulation of cells is to isolate a 'side population' of (stem) cells which can actively transport lipophilic dyes out of the cells by drug-transporter proteins