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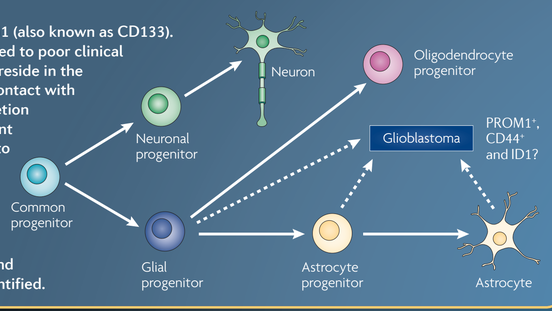
CANCER

The emerging biology of cancer stem cells

The concept of the cancer stem cell (CSC) has taken off rapidly over the past 10 years. CSCs are cells with properties that are similar to those described for tissue stem cells: self-renewal and asymmetric division resulting in the generation of daughter cells destined to differentiate, enabling the regeneration of a tissue. Initial research into the properties of CSCs was based on identifying and verifying markers of this subset of cancer cells. However, most studies have now moved on to understanding the biology of CSCs and the cancers in which they maintain tumour growth, as well as how and why they are able to serially generate a tumour. It is thought that a key element regulating the biology of stem cells is their niche — cells and extracellular matrix that support self-renewal and survival. As we begin to understand the pathways that are crucial for the properties of CSCs, including signals provided by the niche, we will hopefully be able to effectively target this cell population. Linked to the identification of CSCs is the cell of origin. These are cells that when mutated are able to give rise to a tumour. Although these cells may share properties with CSCs, in most cases it is not yet clear whether these cells are one and the same. This poster highlights some of the recent findings regarding the biology of CSCs and the identification of cell types from which cancers can arise.

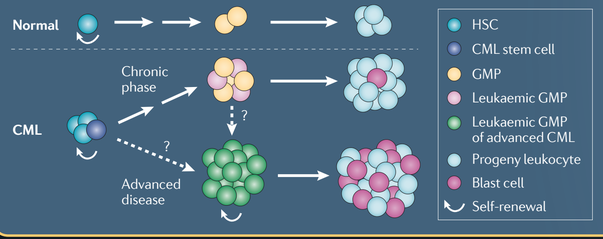
Glioblastoma[1–4]

Glioblastoma stem cells are enriched in a population of cells that express PROM1 (also known as CD133). Although this marker remains controversial, expression of PROM1 has been linked to poor clinical outcome. Glioblastoma is a highly angiogenic tumour, and CSCs are thought to reside in the perivascular niche, where PROM1$^+$ cells have been observed to reside in close contact with endothelial cells. Moreover, PROM1$^+$ cells secrete high levels of VEGF, and depletion of endothelial cells from glioblastoma xenografts suppresses their growth. Recent findings have indicated that stem-like cells in glioblastomas can differentiate into endothelial cells (defined by the expression of CD31 and CD144), thereby contributing to the generation of the tumour vasculature. Several pathways involved in the regulation of stem cell function, such as Notch, TGFβ, sonic hedgehog and hypoxia inducible factors, have also been implicated in regulating glioblastoma stem cell function. Other glioblastoma cells with stem-cell-like characteristics have been shown to express high levels of CD44 and the transcription factor ID1. The cell of origin for glioblastoma has yet to be identified.



Chronic myeloid leukaemia[9]

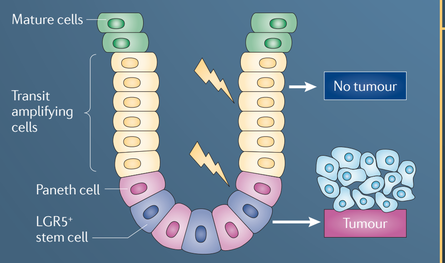
CML cells with *in vivo* repopulating activity display the same surface marker profiles as normal primitive haematopoietic stem cells (HSCs; which are Lin$^-$, CD34$^+$, CD90$^+$ and CD133$^+$ and have aldehyde dehydrogenase activity). Interestingly, CML stem cells with a primitive phenotype are rare, and in patients with chronic phase disease are outnumbered by normal HSCs. CML stem cells also self-renew poorly *in vitro* compared with HSCs, however, the progeny produced by CML stem cells proliferate and survive much better than their normal counterparts, leading to the clinical manifestation of the chronic phase of CML. However, CML stem cells are implicated in disease persistance. Primitive CD34$^+$CD38$^-$ CML cells have an increased expression of BCR–ABL protein that has been linked to genomic instability and resistance to kinase inhibitors. Interestingly, several reports have indicated the emergence of a subclone in blast crisis (the advanced form of CML) that seems to have arisen from a progenitor CML cell. It is currently unclear whether this means that the 'CML stem cell' can change between chronic phase and blast crisis.



LGR5-positive cells and intestinal cancer[5–8]

Cells within the crypts of the stomach, small intestine and colon that express leucine rich-repeat-containing G protein-coupled receptor 5 (LGR5) are long-lived stem cells. Lineage tracing was used to show that cells that express LGR5 give rise to microadenomas and adenomas when expression of the tumour suppressor APC is lost. Moreover, deletion of *Apc* in the progenitor cell population rarely produced adenomas. PROM1 is a stem cell marker in the mouse small intestine. The distribution of *Prom1* and *Lgr5* largely overlap and PROM1 cells can give rise to all cells of the small intestinal epithelium. In genetically engineered mice prone to developing tumours in the small intestine, these arose from PROM1$^+$ cells.

Importantly, LGR5$^+$ cells can give rise to crypt-villus structures *in vitro* that contain stem cells, Paneth cells and all other colonic epithelial cell types. Recent findings have shown that Paneth cells express proteins known to be important for stem cell function, such as WNT, EGF and the Notch ligand delta-like 4. Moreover, Paneth cells seem to be essential for the maintenance of stem cells and crypts in mice. As LGR5$^+$ stem cells can generate Paneth cells, these findings suggest that stem cells can generate their own supporting niche cells, similar to findings in *Drosophila melanogaster*. Thus, a CSC might be capable of similar acts of self-sufficiency and so identifying and understanding the CSC niche would seem to be a priority.

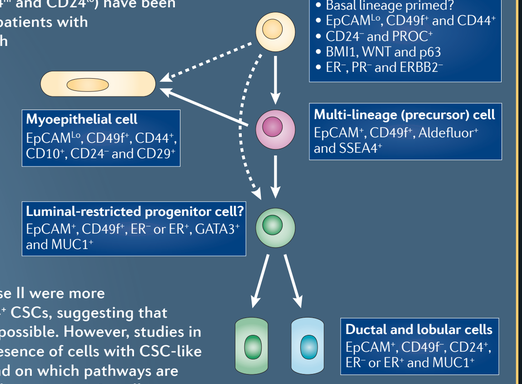


Cell of origin and CSCs[15]

These two terms are often used interchangeably in the literature, but they are not necessarily the same cell. For example, the PROM1$^+$ and LGR5$^+$ stem cells that can generate cancers in the intestine have not yet been shown to be CSCs: the cells that can propagate the tumour when transplanted into a syngeneic mouse. Indeed, even when a more differentiated cell type has been shown to be the probable cell of origin, as has occurred in medulloblastoma, it does not follow that this cell has to have acquired CSC properties. Such a cell may undergo further changes and mutations before a CSC phenotype emerges. Further work is needed in each individual cancer type to establish the relationship between the cell of origin and the CSC.

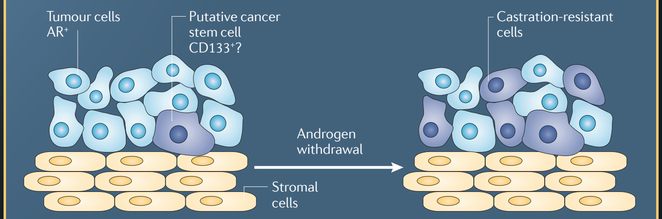
Breast tissue stem cells and cancer[10–12]

Cells with CSC-like characteristics (expression of aldehyde dehydrogenase and CD44^{hi} and CD24^{lo}) have been shown to be enriched in patients with breast cancer treated with chemotherapy, adding weight to the argument that CSCs are a chemoresistant population in a tumour that needs to be targeted. A direct comparison between normal breast tissue stem cells and CSCs indicated that TGFβ1, dynamin, fibronectin, calveolin and casein kinase II were more highly expressed in CD44$^+$ CSCs, suggesting that targeting CSCs could be possible. However, studies in mice indicate that the presence of cells with CSC-like characteristics can depend on which pathways are mutated. Whether this is because certain cell types (stem, progenitor or mature cells) are more susceptible to specific mutations is not clear. As research on breast CSCs has progressed alongside studies of human breast stem cells, it has become apparent that stem cells with different characteristics exist in the breast at different stages of development. Moreover, although stem cells exist in the basal layer, the luminal compartment contains cells from which breast cancer can arise.



Prostate cancer[13,14]

In the normal prostate, epithelial cells with tissue-regenerating capacity that are Sca1$^+$, CD49f^{hi}, TROP2^{hi}, CD44$^+$, CD133$^+$ and CD117$^+$ (mouse) or CD133$^+$, CD44$^+$, CD49f^{hi} and TROP2$^+$ (human) seem to reside in the basal layer of the prostate. However, studies in mice indicate the existence of luminal cells with progenitor characteristics that can regenerate the prostate after androgen withdrawal. As castration resistance is also a property of basal stem cells in the prostate, it suggests a complex cellular hierarchy. Studies in mice indicate that prostate tumours can arise after transformation of basal stem cells and luminal progenitor cells. A subset of cells that are CD133$^+$, $\alpha_2\beta_1{}^+$ and CD44$^+$ and have basal cell characteristics have been shown to be tumorigenic, but whether these cells can serially propagate tumours in mice has yet to be verified.



Abbreviations
APC, adenomatous polyposis coli; AR, androgen receptor; CML, chronic myeloid leukaemia; EGF, epidermal growth factor; ER, oestrogen receptor; GMP, granulocyte macrophage progenitor; hi, high expression levels; lo, low expression levels; MUC1, mucin 1; PR, progesterone receptor; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor.

References
1. Anido, J. *et al. Cancer Cell* **18**, 655–658 (2010)
2. Wang, R. *et al. Nature* **468**, 829–833 (2010)
3. Ricci-Vitiani, L. *et al. Nature* **468**, 824–828 (2010)
4. Huse, J. T. & Holland, E. C. *Nature Rev. Cancer* **10**, 319–331 (2010)
5. Barker, N. *et al. Cell* **127**, 469–480 (2009)
6. Zhu, L. *et al. Nature* **457**, 603–607 (2009)
7. Barker, N. *et al. Cell Stem Cell* **6**, 25–36 (2010)
8. Sato, T. *et al. Nature* **469**, 415–418 (2011)
9. Sloma, I., Jiang, X., Eaves, A. C. and Eaves, C. J. *Leukemia* **24**, 1823–1833 (2010)
10. Lim, E. *et al. Nat Med.* **15**, 907–913 (2009)
11. Molyneux, G. *et al. Cell Stem Cell* **7**, 403–417 (2010)
12. Petersen, O. W. & Polyak, K. *Cold Spring Harb. Perspect. Biol.* 2a003160 (2010)
13. Goldstein, A.S., Stoyanova, T & Witte, O. N. *Mol. Oncol.* **4**, 385–396 (2010)
14. Taylor, R. A., Toivanen, R. & Risbridger, G. P. *Endocrine-related cancer* **17**, R273–R285 (2010)
15. Visvader, J.E. *Nature* **469**, 314–322 (2011)

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