The emerging biology of cancer stem cells

Glioblastoma

Glioblastoma stem cells are enriched in a population of cells that express PROM1 (also known as CD133). Although the expression of CD133 has been linked to poor clinical outcome, glioblastoma is a highly aggressive tumour, and CSCs are thought to reside in the invasive fronts, where CD133+ cells have been observed to reside in close contact with endothelial cells. Moreover, CD133+ cells secrete high levels of VEGF and depletion of mouse glioma xenografts results in growth arrest. Recent findings indicate that stem-like cells in glioblastoma can differentiate into neural cells deficient in the expression of CD133 and CD11b, thereby contributing to the generation of the tumour vasculature. Pathways involved in the maintenance of a stem cell function such as Notch, NF-κB, some hedgehog and hypoxia inducible factors, have also been implicated in regulating glioblastoma stem cell function. Other glioblastoma cells with stem-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.

Breast tissue stem cells and cancer

Cells with CSC-like characteristics, expression of adhesion molecules and CD44+/CD24−, have been shown to be enriched in patients with breast cancer treated with chemotherapy, adding weight to the argument that CSCs are a cellular subset present in a population in a tumour that is not easily targeted. A direct comparison between normal breast tissue stem cells and CSCs indicated that CSCs are dynamic, fibroblast, collagen and carcinoma 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 targeted. A direct comparison between normal breast tissue stem cells and luminal progenitor cells. A subset of cells that are CD133+, 1+ and have the properties of tissue stem cells are suggested 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.

Chronic myeloid leukemia

CML cells within the active regenerating activity display the same surface marker profiles as normal primitive haematopoietic stem cells (HSCs), which are Lin−, CD34+, CD638 and have aldehyde dehydrogenase activity. Interestingly, CML stem cells with primitive features are rare, and in normal HSCs, CML stem cells also self-renew poorly in vitro compared with HSCs; however, the progeny generated by CML stem cells proliferate and survive much better than their normal counterparts, leading to the clinical manifestation of the chronic phase of CML. Moreover, CML stem cells are implicated in disease maintenance. Primitive CD14+CD38− CML cells have an increased expression of BC/ABL protein that can bypass apoptosis and resistance to kinase inhibitors. Interestingly, several reports have indicated the existence of a unique subset of CD14+, CD38− cells, which contain advanced forms of CML that seem to arise from a progenitor CML cell. It is currently unclear whether these cells can change between chronic phase and blast crisis.

LGR5-positive cells and intestinal cancer

Cells within the crypts of the stomach, small intestine and colon that express leucine rich-repeat containin G protein-coupled receptor 5 (LGR5) cells are long-lived stem cells. Lineage tracing of LGR5 cells in female mice show that LGR5+ cells give rise to differentiated epithelial cells and adenosines when expression of the tumour suppressor APC is lost. Moreover, deletion of Apc in the progenitor cells only induced adenomas. LGR5+ stem cells also arise in the mouse small intestine. The presence of Procto and Lp’s largely overlap and PROCTO cells can give rise to all tissues of the small intestine epithelium. In genetically engineered mice prone to developing tumours in the small intestine, these arise from PROCTO+ cells. Importantly, LGR5+ cells can give rise to crypt-villus structures in vitro that contain stem cells, Paneth cells and all other colonies epithelial cell types. Recent findings have shown that Paneth cells express proteins known to be important for stem cell function, such as WNT1, EGFR 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 the CSC niche would seem to be a priority.

Prostate cancer

In the normal prostate, epithelial cells with tissue-regenerating capacity that are Sca1+, CD44+, TROP2+, CD133+ and CD117+ (mouse or CD134+, CD44+, 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 problem of breast 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 breast CSCs is also CD133+ 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.

Cell of origin and CSCs

Two recent studies are often placed interchangeably in the literature, but they are not necessarily the same cell. 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 mouse. 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.