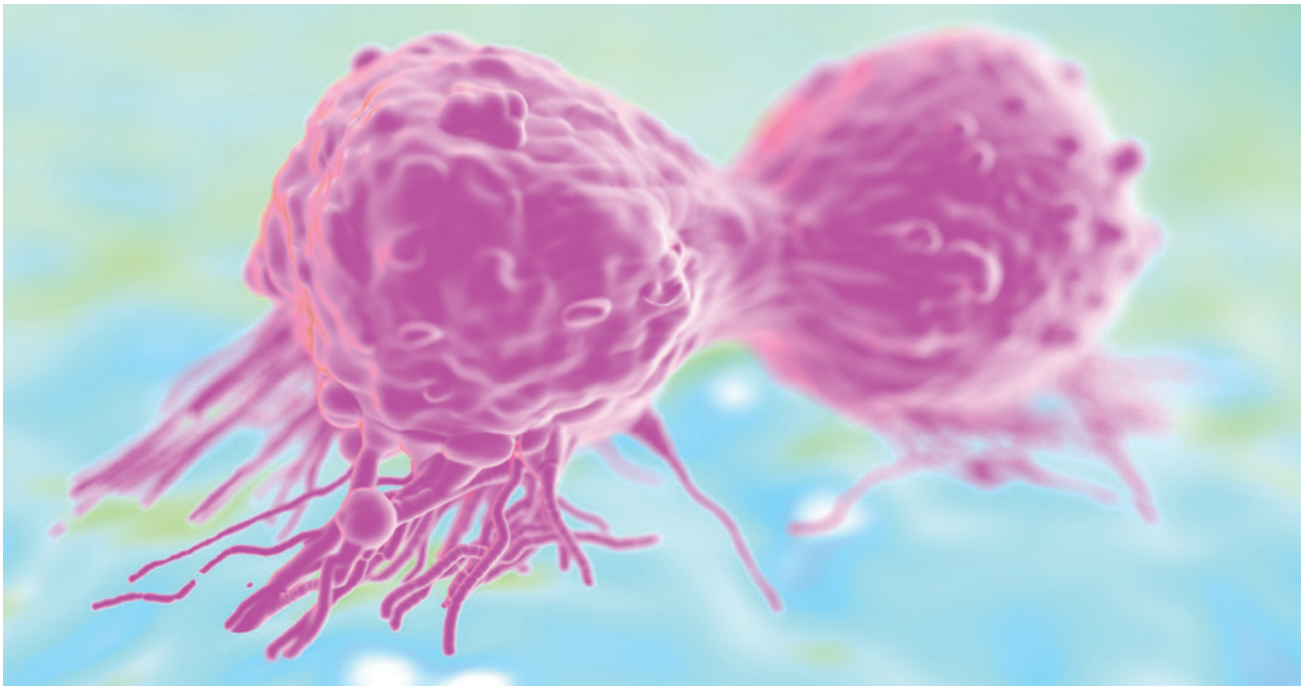

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Stemming the Tide

As a multi-factorial disease, the successful treatment of cancer requires a combination of therapies to target the tumour. However, current strategies often fail to take into account the presence of cancer stem cells, thus remaining limited in their efficacy

Jenny Worthington at Axis BioServices

With the global spend on oncology medicines continuing to rise, this market remains highly attractive to both large and small R&D companies that demonstrate increasingly innovative approaches to cancer therapy. The boom of molecular-targeted agents for cancer therapy has resulted in a number of successful compounds being brought to market; however, in the clinic, patients continue to suffer from tumour recurrence and fatal metastatic spread. One reason for the failure of current therapies is thought to be the presence of cancer stem cells (CSC) within the tumour tissue. These CSCs are one of the 'hot' new targets for cancer therapeutics.

What are CSCs?

CSCs are a rare population of cells – 1-3% depending on tumour type – that exhibit unique features, making them essential for the establishment and recurrence of tumours. They self-renew (divide to form new stem cells), are immortal, and are pluripotent (can generate tumour cells with various phenotypes) – which all result in the growth of primary tumours.

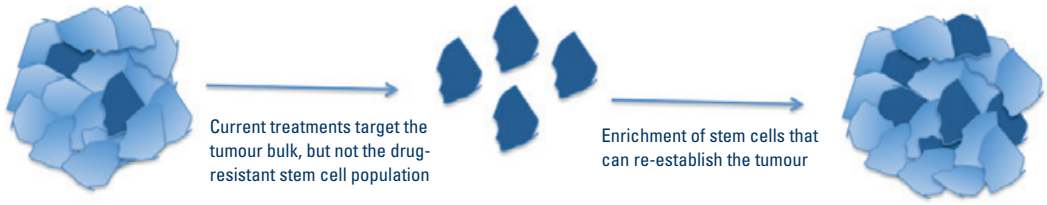
Although CSCs comprise only a small proportion of the tumour mass, their properties make them extremely important in the tumour response to treatment. Current therapies are based on their ability to kill the majority of tumour cells; however, CSCs exhibit resistance to both radiotherapy and chemotherapy through a range of mechanisms, including lower levels of reactive oxygen species, the nuclear factor-κβ (NF-κβ) pathway and increased cell surface expression of CD44. Regardless of the mechanisms involved, current treatments may kill the bulk of the tumour, but at the same time, they enrich the drug-resistant CRC population – eventually leading to tumour regrowth (see Figure 1, page 28). In addition, it has been demonstrated in a range of tumour types that tumours containing CSCs have a higher propensity to metastasize; elimination of the CSC population eradicates the metastatic phenotype.

Although CSCs were identified some time ago, it is only in the last decade that research has intensified into their role in cancer biology. Their intrinsic properties make them a key factor in tumour aggressiveness and resistance to therapy, and they are therefore an excellent target for cancer treatment. Despite the fact that, in many ways, research is still in its infancy, the overwhelming evidence points to CSCs as a major driver in tumour progression – implying that future cancer treatment regimens should incorporate a CSC-targeting agent in some form.

Targeted Therapies

Research into CSCs has identified a number of key areas where therapeutic agents can, and have been, developed to target

Figure 1: Current treatments target 'normal' tumour cells, but not the resistant stem cell population. These cells can then self-renew and divide to generate tumour cell types of various phenotypes, resulting in recurrence of the tumour



CSCs. Some of these strategies have resulted in clinical trials, while most are still at the preclinical stage.

Identification of CSCs from a population of tumour cells is possible due to alterations in cell surface markers. These markers include CD33, CD44, CD90, CD133, IL-3R and TIM-3. Antibodies have been developed against many of these targets and have demonstrated significant ability to specifically affect stem cells within a range of tumour types. For example, gentuzumab ozogamicin – a humanised anti-CD33 monoclonal antibody – has been used in an antibody-drug conjugate with calicheamicin to treat acute myeloid leukaemia, while a similar approach using an anti-CD44 antibody conjugated with gold nanorod has targeted breast cancer cells.

One of the most common cell surface markers used to identify CSCs is CD133. This was originally identified as a marker in leukaemia cells, but has recently been demonstrated to be present in many malignancies including colon, lung, breast, prostate, pancreas and glioma. Many scientific articles have described targeting CD133 with antibodies or RNAi approaches, as this can impair the pro-tumour effects of CSCs.

When discussing targeting cell surface makers, it is worth noting that CSCs exhibit plasticity, which is the ability to differentiate into cell types with different phenotypic lineages. This property may, at least in part, explain the heterogeneity of cells found within tumours. It is likely, therefore, that targeting CSCs solely on the basis of cell surface markers, which may change under a variety of environmental and temporal conditions, is a potential therapeutic pitfall.

Trial Stage

As is the case for many different cancer cell types, dysregulation of signalling pathways is crucial for CSCs in maintaining their typical characteristics. These may also allow for a more precise targeting mechanism. Among the signalling cascades that have been targeted are β-catenin, Hedgehog, JAK/STAT, Notch, NF-κβ, FAK and PI3K.

FAK has been identified as a critical component in tumour establishment and progression; Verastem's FAK-inhibitor VS-6063 is currently in clinical trials for mesothelioma, ovarian and other solid tumours. Meanwhile, Boston Biomedical has two CSC-targeting compounds that are currently advancing through clinical trials: BBI608, which targets the STAT3 pathway, is in Phase 3 for colorectal and gastric cancer; and BBI503, which targets Nanog and other pathways, is in Phase 2 for a range of solid tumour types. Oncomed has also developed a range of monoclonal antibodies that target pathways in CSCs, and their drug tarextumab is undergoing Phase 2 trials in pancreatic and small cell lung cancer; this antibody targets Notch 2/3.

Other Strategies

As an alternative to targeting cell signalling pathways within cells, manipulating the tumour microenvironment has become a popular strategy for targeting both CSCs and tumour cells in general. It is now widely recognised that stromal cells play an integral part in disease progression by secreting factors that stimulate cell growth, drug resistance and metastatic spread. In leukaemia, secreted CXCL12 and its receptor CXCR4 have been shown to be important for maintenance of cancer cells in the bone marrow where they are resistant to chemotherapy. The first-in-class CXCR4 antagonist Plerixafor disrupts this signalling axis, resulting in leukaemia cells leaving the bone marrow microenvironment and exhibiting sensitivity to therapy.

Another important feature of the tumour microenvironment is hypoxia, or low oxygen concentration. Studies have shown that, in solid tumours, CSCs are predominantly found in the perivascular area and surrounding necrotic area, where they flourish in hypoxic conditions. This suggests that using hypoxia-targeting drugs may be a useful strategy in treating CSCs; however, this remains to be confirmed.

Another approach which is somewhat linked to that of targeting hypoxia involves the use of anti-angiogenics. This class of drug, which includes bevacizumab, targets and disrupts tumour vasculature, resulting in decreased tumour growth. Studies have shown that in a glioma model, treatment with bevacizumab saw a decline in CD133+ cells, implying a reduction in CSCs. However, disruption of tumour vasculature encourages increased tumour hypoxia, which many studies have shown leads to a rise in CSCs; thus highlighting the need for further research into the area of CSCs.

Multifunctional efflux transporters are only one cause of chemoresistance in tumour cells, but are by far the most studied. ATP-binding cassette (ABC) proteins protect CSCs from chemotherapy and are often over-expressed, thus ensuring that these cells can survive chemotherapy insults and repopulate the tumour. It has been shown that ABC inhibitors can reduce the number of CSCs in some tumour types, although much more research is needed in this area.

The major issue with the therapeutic strategies described above is that they are not specific to CSCs, instead targeting tumour or stem cells in general. Further studies are needed in the area of CSCs to identify differences between cancer and normal stem cells, because these are the targets that would offer treatment specificity. The small numbers of CSCs within the tumour population make this type of research very difficult, but crucial in improving our understanding of the biology of these cells and identification of how they can be targeted for cancer therapy.

Furthering Understanding

Although stem cell research is currently a hot topic in both basic biology and drug discovery, there are a number of areas that are still to be fully understood. These include the relationship between stem cells and tumour cells in the early stages of cancer development, the role of CSCs in disease recurrence, and identifying pathways or markers that differentiate CSCs from normal stem cells. Further understanding these characteristics will undoubtedly aid in the development of agents that specifically target CSCs and reduce potential side-effects and treatment failures.

It is also worth considering the role that targeting CSCs will play in cancer therapy. It is extremely unlikely that CSC-targeting agents will be used as a monotherapy in the clinic. Rather, as a multifactorial disease, it is likely that cancer will only be successfully treated by a combination of therapies targeting both aberrant pathways and environmental conditions that exist in these tumours. By fully understanding the molecular and phenotypical changes that occur within tumours during treatment with various classes of drug, intelligent scheduling of different targeting agents at different times will be possible, increasing the likelihood of successful outcomes.

About the author

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