CANCER STEM CELLS

Targeting the root of cancer relapse

Hypermalignant cancer cells, or cancer stem cells (CSCs), have been identified in a range of different types of cancer. CSCs have a high potential to metastasize and, owing to their resistance to chemo- and radiotherapy, they often cause relapse after treatment. Now, reporting in *Proc. Natl Acad. Sci. USA*, Li *et al.* show that the small molecule BBI608, an inhibitor of signal transducer and activator of transcription 3 (STAT3), is active against CSCs and blocks cancer metastasis and relapse in animal models.

CSCs are difficult to kill — they overexpress drug efflux pumps and have an increased capacity to activate anti-apoptotic and pro-survival pathways as well as DNA repair. Therefore, chemotherapeutics tend to de-bulk tumours, but they potentially enrich for CSCs in the process. Previous strategies to develop drugs against CSCs have predominantly focused on identifying unique cell-surface markers that can be targeted. The authors took a different approach — by aiming to target the factors that support cancer cell 'stemness'. They had previously found that the transcription factor STAT3 is crucially important for maintaining the stemness of CSCs and, using computational biology in combination with phenotypic screening, they identified BBI608 as a specific inhibitor of STAT3.

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In a xenograft model of human pancreatic cancer, treatment with the chemotherapeutic agent gemcitabine for 41 days led to tumour regression, but tumours quickly relapsed after treatment cessation. By contrast, BBI608 (injected intraperitoneally) not only inhibited tumour growth but also prevented tumour relapse post-treatment, without inducing toxicity. To test whether BBI608 indeed kills CSCs, the authors analysed single-cell suspensions of tumours from mice that had been treated with either BBI608 or gemcitabine for 7 days. Compared with tumours from control mice, gemcitabine appeared to enrich CSCs threefold, whereas BBI608 reduced CSCs fivefold. Similar results were obtained in a head-and-neck tumour model. In the intrasplenic nude mouse model system (ISMS), a model for spontaneous metastasis, treatment with BBI608 completely blocked the development of any metastases.

Ensuing *in vitro* experiments with a range of different cell lines showed that both CSCs and non-stem cancer cells were killed by BBI608, whereas the chemotherapeutic doxorubicin and the targeted kinase inhibitors imatinib, sunitinib and erlotinib only killed the non-stem cancer cells. Biochemical analysis showed that BBI608 induces a dose-dependent decrease in the expression of genes and production of proteins that are implicated in CSC self-renewal, whereas chemotherapeutics either had no effect or increased CSC gene expression. Normal adult haematopoietic stem cells were not affected by BBI608.

STAT3 is known to be essential for the maintenance of embryonic, but not adult, stem cells. The authors suggest that CSCs 'hijack' STAT3 and thereby become highly sensitive to its inhibition. BBI608 has shown good tolerability and activity in Phase I clinical trials and is therefore a promising candidate for a new generation of cancer therapeutics that prevent relapse and metastasis.

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ORIGINAL RESEARCH PAPER Li, Y. *et al.* Suppression of cancer relapse and metastasis by inhibiting cancer stem cells. *Proc. Natl Acad. Sci. USA* http://doi/10.1073/pnas.1424171112 (2015).
FURTHER READING Langleben, A. *et al.* A dose-escalation Phase I study of a first-in-class cancer stemness inhibitor in patients with advanced malignancies. *J. Clin. Oncol.* (meeting abstracts) **31** (Suppl. 15), 2542 (2013) | Hitron, M. *et al.* A Phase 1b study of the cancer stem cell inhibitor BBI608 administered with paclitaxel in patients with advanced malignancies. *J. Clin. Oncol.* (meeting abstracts) **32** (Suppl. 15), 2530 (2014)