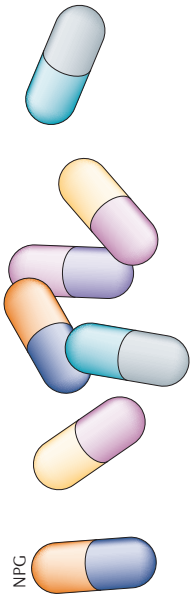
ANTICANCER DRUGS

Antipsychotic to anticancer agent?



The selective targeting of cancer stem cells (CSCs) to induce either differentiation or apoptosis remains an attractive therapeutic approach, even though there is uncertainty about precisely what defines a CSC. A new study has devised a high-throughput platform to screen for compounds that selectively differentiate CSC-like cells and has identified dopamine receptor antagonists as promising candidates.

To model normal stem cells and CSCs, Mickie Bhatia and colleagues used normal human embryonic stem cells and a neoplastic variant of these cells that has various properties of CSCs (CSC-like cells). Both cell lines were transduced with a fluorescent reporter to detect the loss of expression of the OCT4 pluripotency marker, thus allowing high-throughput screening for compounds that selectively induce differentiation in the CSC-like cells.

In an initial screen of 590 well-characterized compounds, the authors identified the antipsychotic drug thioridazine as the most promising hit on the basis of the degree of selectivity for CSC-like cells. As evidence of the robustness of the system, an expanded screen of 2,446 compounds identified not only thioridazine, but also two other chemically similar compounds. Furthermore, the additional identification of rapamycin and lestaurtinib — compounds with known antileukaemic properties — suggested that this screen in embryonic cells might have biological relevance to leukaemia stem cells.

In further tests the authors found that thioridazine reduced the ability of human acute myeloid leukaemia (AML) samples to proliferate and to self-renew, as shown by a decrease in both the ability of the treated cells to form colonies *in vitro* and in the efficiency of transplantation into recipient mice. These effects were accompanied by differentiation, as shown by the induction of CD11b (also known as integrin αM) expression. Moreover, thioridazine showed synergy with cytarabine (a standard treatment for AML) for eliminating the colony-forming ability of AML samples. By contrast, normal human haematopoietic stem cells (HSCs) from cord blood were relatively unaffected by thioridazine treatment, maintaining their abilities to form colonies *in vitro* and to engraft recipient mice, where they reconstituted all haematopoietic lineages. HSCs also showed less synergy between thioridazine and cytarabine.

Thioridazine exerts its antipsychotic effects by antagonizing dopamine receptors. Consistent with the same receptors being important for CSC functions, dopamine receptors were found to be upregulated in human AML samples versus normal HSCs. Additionally, among the AML samples, higher expression correlated with a worse clinical outcome and increased efficiencies of transplantation into mice. Furthermore, when AML cells were sorted into subpopulations with and without dopamine receptor expression, thioridazine only affected the colony-forming ability of dopamine receptor-positive cells. There was also evidence of dopamine receptor upregulation in the CSC population (as defined by cell surface markers) in breast cancer samples.

Because drug treatments in this study were carried out *in vitro*, it will be important to determine whether the anticancer potential of dopamine receptor targeting will be realized using *in vivo* treatments, and whether effects on CSCs can be separated from neurological effects. Given that AML seems to have a high proportion of CSCs compared with most other cancers, it will be crucial to assess whether efficacy can be achieved in treating established solid tumours. Interestingly, epidemiological evidence suggests that patients with impaired dopamine receptor signalling — owing to thioridazine treatment for psychosis or to Parkinson's disease — may have a lower incidence of various cancers.

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ORIGINAL RESEARCH PAPER Sachlos, E. *et al.* Identification of drugs including a dopamine receptor antagonist that selectively target cancer stem cells. *Cell* 24 May 2012 (doi:10.1016/j.cell.2012.03.049)