Chemical biology

Double-headed molecule reprograms cancer cells

James D. Phelan & Louis M. Staudt

Molecules have been developed that switch a transcription factor from being a repressor of gene expression to an activator — and thereby able to kill cancer cells. The findings offer a fresh strategy for designing anticancer drugs. See p.417

Cancer cells acquire genetic alterations that reprogram the expression of thousands of genes, to promote rapid cell growth and block pathways that induce cell death. On page 417, Gourisankar *et al.*[1] report molecules that transform BCL6, a protein that promotes cancer by repressing the transcription of various genes, into a transcriptional activator. The molecules used to induce this transformation constitute a new class of compound for investigation as potential anticancer drugs.

BCL6 functions as a master regulator of immune cells known as germinal centre B cells — which arise during normal immune responses, but are also the cells of origin for a type of cancer called diffuse large B cell lymphoma (DLBCL). More specifically, BCL6 directly represses genes that encode cell-cycle inhibitors and proteins that are involved in a form of programmed cell death known as apoptosis. This protects germinal centre B cells and DLBCLs from stress caused by a process of programmed mutation (immunoglobulin somatic hypermutation) that allows the immune system to respond effectively to organisms that cause diseases[2]. Moreover, BCL6 maintains the identity of germinal centre B cells, preventing them from irreversibly differentiating into plasma cells by repressing the gene that encodes the transcription-repressing protein BLIMP-1 (ref. 3). BCL6 is frequently dysregulated in DLBCLs, and thereby maintains the cancer cells in a highly proliferative state.

Gourisankar and colleagues decided to try to alter the transcriptional effects of BCL6 by building on a concept known as chemically induced proximity (CIP). CIP uses a core principle of cell biology — namely that cellular regulation often involves mechanisms that induce two different proteins to come close together[4]. For example, the natural process of protein turnover involves a step known as ubiquitination, which marks a target protein for degradation; this step is mediated by an adaptor protein that binds both the target and the enzyme that catalyses ubiquitination, thereby bringing them together. This turnover process has been harnessed for therapeutic purposes by constructing small molecules called PROTACs, which carry out the function of the adaptor to target specific proteins for degradation[5].

In their study, Gourisankar *et al.* synthesized a compound in which a BCL6-binding molecule[6] is connected to another molecule that binds BRD4, a protein that activates transcription[7]. This first-in-class compound forms a complex with BRD4 and BCL6 on BCL6-binding sites in the genome, thereby allowing BRD4 to potently activate the expression of genes that are normally silenced by BCL6 (Fig. 1). The authors named their compound TCIP1, where TCIP stands for transcriptional/epigenetic chemical inducer of proximity. As the authors had hoped, TCIP1 treatment of cell lines derived from DLBCLs upregulated the expression of hundreds of genes, many of which are known to be targeted by BCL6. Even more excitingly, TCIP1 potently kills BCL6-expressing DLBCL cells *in vitro*, suggesting that TCIPs should be investigated further as a potential new class of anticancer drug.

Numerous compounds have been identified that inhibit or degrade BCL6, thereby alleviating repression of its target genes and killing DLBCL cells *in vitro*[8]. However, because such compounds work through a 'loss of function' mechanism, they can require near-complete BCL6 inhibition to be effective. By contrast, TCIP1 uses a 'gain of function' mechanism, which means that only a fraction of cellular BCL6 might need to be engaged to exert the compound's effects. This might be helpful for treating large and poorly vascularized tumours in which it is difficult to achieve high drug concentrations.

Gourisankar *et al.* observed that, as well as upregulating the expression of many tumour-suppressor genes, TCIP1 also downregulates *MYC* (a tumour-promoting gene that encodes a transcription factor) and many of its transcriptional targets — which might contribute to the exceptional toxicity of this agent for lymphoma cells. The mechanisms underlying *MYC* downregulation by TCIP1 are unclear, but one possibility is that the compound upregulates the BCL6 target BLIMP-1, which then represses *MYC* (ref. 3). Alternatively, TCIP1 might recruit BCL6 to some BRD4-targeted genes, including *MYC* (ref. 9), thereby repressing their expression. This mechanistic complexity illustrates that TCIPs need to be carefully vetted experimentally to discern how they alter gene expression and biological outcomes.

The new study highlights the potential of TCIP1 as a DLBCL therapy, but more work is needed to determine which subtypes of this cancer will respond. This could be dictated by the transcription-repressing activity of BCL6, which is highest in one genetic subtype of DLBCL (the EZB subtype)[10]. Importantly, TCIP1 might have clinical activity in other BCL6-expressing lymphomas, such as follicular lymphoma and Burkitt lymphoma, and in

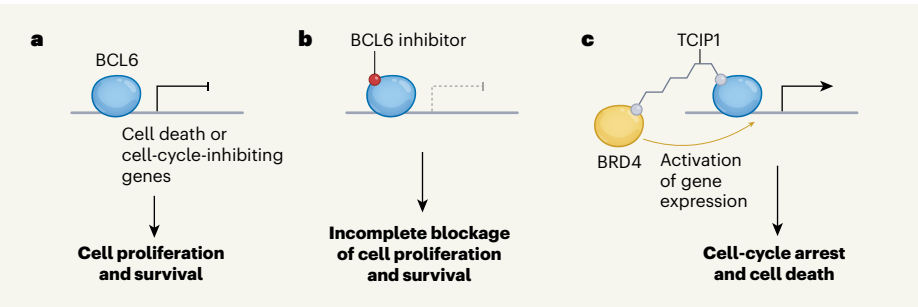

Figure 1 | A strategy for changing the effects of a transcription factor. a, The transcription factor BCL6 represses the expression of genes that encode cell-cycle inhibitors and proteins that promote programmed cell death. It promotes the proliferation and survival of certain cancer cells. **b**, Compounds that inhibit BCL6 or promote its degradation have been reported as potential anticancer agents, but cell proliferation and survival are incompletely blocked unless all the BCL6 molecules are inhibited or degraded. **c**, Gourisankar *et al.*[1] synthesized a compound called TCIP1, in which a BCL6-binding group[6] is connected to another group that binds BRD4, a protein that activates transcription. TCIP1 forms a complex with BRD4 and BCL6 on BCL6-binding sites in the genome, thereby allowing BRD4 to potently activate the expression of genes that are normally silenced by BCL6. In this way, TCIP1 potently kills BCL6-expressing cancer cells *in vitro*.

angioimmunoblastic T cell lymphoma (which is derived from BCL6-expressing immune cells known as T follicular helper cells).

When developing a new agent as an anticancer drug, an early consideration is how to pair it with approved drugs to achieve mechanistic synergy and better clinical efficacy. Given that TCIP1 induces the expression of the pro-apoptotic BIM and NOXA proteins, it seems logical to pair it with other agents that promote apoptosis. On the flip side, because TCIP1 induces cell-cycle arrest, it might counter the effect of some anticancer agents that require progression of the cell cycle for their efficacy.

Another crucial consideration when evaluating new anticancer drugs is the possibility of producing unacceptable clinical side effects. In the case of TCIP1, there are reasons for concern because BCL6 is expressed in cells of the innate immune system and because genetically engineered mice that lack BCL6 experience severe inflammation[11,12]. The authors addressed this issue head on and found no evidence of TCIP1-induced inflammation in treated wild-type mice — not even in the spleen, in which upregulation of BCL6-targeted genes was particularly high. Nonetheless, clinical trials of TCIP1 or related molecules should watch out for possible inflammatory side effects.

How generally applicable is the TCIP approach? Transcription factors are frequently dysregulated in cancer, but, unlike BCL6, the majority of these factors activate transcription. Any TCIP designed to target these factors would therefore need to recruit a transcriptional repressor — which in principle is no more difficult to do than recruiting an activator. Another consideration when choosing a transcription factor to target with a TCIP is the relative activity of that factor in malignant versus non-malignant cells. High cancer specificity might be possible in some cases, but not in others. Overall, the development of TCIPs will be limited only by the imagination of cancer biologists and the innovation of chemists. Such efforts promise to end the perception that cancer-promoting transcription factors cannot be targeted by drugs.

"TCIP compounds should be investigated further as a potential new class of anticancer drug."

James D. Phelan and **Louis M. Staudt** are in the Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
e-mail: lstaudt@mail.nih.gov

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