IMMUNOTHERAPY

Designer siRNA

RNA interference — a process by which short RNA oligonucleotides silence the expression of specific target genes — has received much attention as a potential approach for the treatment of numerous diseases, including cancer. However, the specificity of this approach was thought to be compromised by the fact that short RNA molecules trigger certain innate immune receptors that are normally dedicated to sensing viral infection. Now, Poeck *et al*. have turned this unintentional off-target effect to their advantage and have designed a short interfering RNA (siRNA) that acts as a potent antitumour agent not only by silencing the expression of the anti-apoptotic gene *Bcl2* (B-cell lymphoma 2) but also by triggering the innate immune receptor RIG-I (retinoic-acid-inducible gene I) to induce an antitumour immune response.

RIG-I is known to detect RNA molecules that contain 5′-triphosphate groups. Incorporation of a 5′-triphosphate group into *Bcl2*-specific siRNAs to confer immunostimulatory properties showed better therapeutic activity in the B16 melanoma lung metastasis model in mice than siRNAs that were designed to only activate RIG-I or silence *Bcl2* expression. The observed antitumour activity depended on the triggering of RIG-I (and not other RNA-specific innate immune receptors) in dendritic cells and on intact type I interferon (IFN)-receptor signalling. Natural killer cells also proved to be important in the enhanced antitumour immune response. Importantly, 5′-triphosphate-siRNA also activated RIG-I in the B16 melanoma cells, leading to a type I IFN response and to increased susceptibility to apoptosis caused by *Bcl2* downregulation, although 5′-triphosphate-siRNA did not compromise the survival of immune cells.

The contribution of *Bcl2* gene silencing to the therapeutic effect was confirmed by showing that expression of a mutated *Bcl2* construct that was not targeted by the *Bcl2*-specific 5′-triphosphate-siRNA rescued the B16 melanoma cells from apoptosis induction and reduced the *in vivo* efficacy of the *Bcl2*-specific 5′-triphosphate-siRNA.

Finally, the observation that this dual-acting siRNA was also effective at promoting the apoptosis of a human melanoma cell line provides hope that this approach could be applied to the treatment of human disease.

Lucy Bird

ORIGINAL RESEARCH PAPER Poeck, H. *et al.* 5′-triphosphate-siRNA: turning gene silencing and Rig-I activation against melanoma. *Nature Med.* **14**, 1256–1263 (2008)
FURTHER READING Petrocca, F. & Lieberman, J. RIG-ing an antitumor response. *Nature Med.* **14**, 1152–1153 (2008)