Non-viral cancer gene therapy – what is best? ▼

In the July issue of *Drug Discovery Today*, Spack and Sorgi [1] pointed out the importance of unmethylated CpG motifs in plasmid DNA (pDNA) for use in cancer gene therapy. This is based on a mammalian immune defense mechanism against bacteria, where inflammatory cytokines are released in response to these sequences. We would like to thank the authors for highlighting this important phenomenon in non-viral gene delivery. We agree that these unmethylated CpG sequences have both advantages and disadvantages in gene therapeutic approaches. We would also like to expand this discussion here.

In a recent publication [2], unmethylated CpG sequences were not the only cause of this inflammatory response; other CpG-independent pathways of activating immune cells were also observed *in vitro*. At least two possibilities can be suggested: DNA aggregation, for example when complexed with cationic lipids of (poly)cationic carriers, or a mechanism triggered by the combination of lipidic components and CpG motifs.

The removal of unmethylated CpG sequences, for example by alternative codon usage or growing plasmids in eukaryotic micro-organisms, will be helpful, or even crucial, for certain gene therapeutic protocols, like the treatment of cystic fibrosis. Conversely, treatment of malignant disease could benefit from combinations of gene therapeutic concepts with other conventional chemotherapy, radiation therapy or cytokine therapies. In this respect, a CpG-based stimulus of the immune system when focused to the target site can be advantageous.

We take this opportunity to highlight our recent observation that specific targeting to the tumour is possible. Local expression of tumour necrosis factor α (TNFα) within tumours was observed after systemic delivery of the vector and was not accompanied by elevated levels of TNFα in the bloodstream [3]. Only if the delivery vector was interacting with blood components and, thereafter, captured in the lung, were elevated levels of TNFα observed in lung and plasma.

Cancer gene therapy is still considered to be in an infant state. Initially, the major challenge was to achieve delivery of pDNA to the tumour by by-passing the defense mechanism, for example the complement cascade and unspecific interactions with blood components. Obviously, further refinement and discussion are necessary to make cancer gene therapy more successful.

References

1 Spack, E.G. and Sorgi, F.L. (2002) The double-edged cytokine sword of non-viral gene targeting to tumors. *Drug Discov. Today* 7, 754–755

2 Yasuda, K. *et al.* (2002) Plasmid DNA activates murine macrophages to induce inflammatory cytokines in a CpG motif-independent manner by complex formation with cationic liposomes. *Biochem. Biophys. Res. Commun.* 293, 344–348

3 Kircheis, R. *et al.* (2002) Tumor-targeted gene delivery of tumor necrosis factor-alpha induces tumor necrosis and tumor regression without systemic toxicity. *Cancer Gene Ther.* 9, 673–680

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