necrosis factor inhibitors, which can be considered as a major breakthrough in the treatment of RA[1,2]. Interleukin-1 (IL-1) also plays a major role in the pathogenesis of RA and its natural inhibitor, the IL-1-receptor antagonist (IL-1Ra), ameliorates the course of the disease in several experimental models of arthritis. The administration of IL-1Ra is associated with significant improvement in disease activity and a reduction in the frequency and severity of radiological signs of joint damage[3,4]. However, the systemic administration of biological agents has important limitations primarily due to their high cost to produce.

The local delivery of cytokines or other mediators by gene therapy can overcome some of the limitations associated with the systemic administration of biological agents. Therapeutic products can be synthesized in disease tissues in high quantities and consumed locally, thus having only limited effects systematically. In a recent issue of *Drug Discovery Today*, Ghivizzani *et al.* provided an excellent overview of the different approaches to direct local gene delivery[5]. Previously, this group has published several studies in which *in vitro* transduced synovial fibroblasts were transplanted into the joints to produce cytokines or soluble receptors. Using this *ex vivo* gene therapy strategy, the authors successfully treated several experimental models of arthritis. In addition, they conducted the first clinical trial in patients with RA[6].

Clinical relevance

What should we expect of gene therapy to consider this approach as clinically relevant for the treatment of RA? It should provide a high level of expression of the transgene in disease tissues and this production should be long-lasting. In addition, the procedure should be easy, widely available and safe. Another problem is that RA is, by definition, a polyarticular disease. Hence, it will be important to obtain the expression of therapeutic genes in several joints. Unfortunately, as mentioned by the authors, most of these issues are not resolved yet.

The paper is divided into two parts in which they reviewed in detail the advantages and limitations of virally mediated and non-virally mediated methods of local gene delivery. Vectors derived from viruses have several limitations such as immunogenicity, which leads to short-term expression by adenoviral vectors, and lack of effective infection by retroviral vectors, which only infect dividing cells. Some of these problems can be overcome using other vectors such as the lentiviral vector, which can infect non-dividing cells. However, the potential risk of insertional mutations due to integration of additional virus sequences into the host genome is a concern. Non-viral gene therapy is another interesting approach. The authors presented some of their studies on different DNA formulation. Unfortunately, their results show that the expression of the transgene was also very short. The levels of IL-1Ra were elevated only 24 h after the injection and were undetectable after 48 h. In addition, the occurrence of an inflammatory reaction following the injection of DNA is another potential concern.

Conclusion

In conclusion, the local delivery of therapeutic genes in disease tissues is very attractive and has numerous advantages over classic drug therapy. However, as mentioned by the authors, a considerable quantity of work remains to be performed before gene therapy moves from the bench into the clinic for the treatment of RA.

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Wither solid-phase chemistry? – Reply ▲

Initial letter: Terrett, N. (2001) *Drug Discovery Today* 6, 16

Response from Mark Bradley

What is the balance between solid- and solution-phase chemistry? This is hard to judge with so many different philosophies and approaches, but I do not think it is as stark as Nick Terrett portrays. For example, a recent review by Roland Dolle[1] actually showed that, although solution methods accounted for 50% of total libraries produced and reported in 1996, this was a peak, and solution-phase synthesis of libraries has since fallen to 33% in 1997 and 1998 and to just 20% in 1999. Another example of the continued power of solid-phase chemistry is the runaway success of Irori (almost an industry standard now) and the recent advent

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of Irori NanoKan methodology for making very large solid-phase-based libraries.

This shows, I feel, that solid-phase chemistry is still playing a major role in library synthesis. In addition, the line between solid-phase and solution-phase is becoming much less distinct with the use of resin-based reagents and scavengers, with methods such as 'catch and release' being a clear hybrid between the two techniques. Thus, for synthetically complex compounds, large compound numbers, and for enhancing solution-phase synthesis, solid-phase chemistry has a number of unique and clear advantages and is still alive and well.

Reference

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