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Cover Story

Efficient delivery of VEGF via heparin-functionalized nanoparticle–fibrin complex

Regeneration of tissues requires formation of new blood vessels to supply nutrients and oxygen. The angiogenesis process is regulated by various growth factors, and one of the most important and widely studied growth factors is vascular endothelial growth factor (VEGF). Because of its short half-life, VEGF has been formulated into various sustained release delivery systems. The long-term VEGF delivery is usually based on encapsulation of the drug in biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA). Although such systems are designed to release the loaded protein in a sustained manner following the degradation of the polymer, they often exhibit much faster release than expected with the high initial burst release. To achieve better sustained release, VEGF has been conjugated with heparin. Heparin-functionalization was used to secure the loaded growth factor and release it in a biologically relevant manner [1].

A new approach for sustained release of VEGF was described in an article by Professor Tae and his colleagues in this issue [2]. In the study, the authors applied the heparin-functionalized nanoparticle–fibrin gel complex (NP–Fibrin) for efficient delivery of VEGF (VEGF–NP–Fibrin) aimed for angiogenesis. Instead of loading a protein inside the PLGA particles, the authors utilized PLGA nanoparticles as a core that can be coated with heparin/Pluronic layer, which in turn, interact with VEGF. The system was then loaded inside the fibrin gel for sustained release. This NP-Fibrin could suppress the initial burst of the loaded VEGF to the 30% level and sustain its release over several weeks *in vitro*. Furthermore, VEGF–NP–Fibrin strongly enhanced the therapeutic angiogenic effect in a rabbit ischemic hind limb model with a relative small amount (2.5 μg) of VEGF; VEGF–NP–Fibrin resulted in a significant increase in the recovered calf blood pressure, the angiographic score, and the density of collaterals, as compared with VEGF–Fibrin or Fibrin.

Regarding the use of VEGF in revascularization, a number of studies have reported that a therapeutic strategy based on a single VEGF treatment may be insufficient to induce functional and stable vessels for the treatment of ischemic diseases. Thus, effective therapeutic strategies based on multiple growth factors (e.g., VEGF and bFGF or VEGF and PDGF) have been suggested. In contrast to the published reports, however, Professor Tae's group did not find any indication of regression for their long-term results (i.e., 4 weeks after implantation and at least 2 weeks after degradation of the implant). Angiographic and histological analysis showed that collaterals developed from VEGF–NP–Fibrin remained stable, even though the initially implanted NP-Fibrin have already been degraded and disappeared within 2 weeks in the rabbit intramuscular pockets. Thus, the developed collaterals remained stable at least for 2 weeks after formation. Their results point to the therapeutic potential of single VEGF dosage as an effective treatment of ischemic disease if administered via an efficient delivery system.

The VEGF–NP–Fibrin system was highly effective in delivering VEGF for over a month. One of the advantages of the NP–Fibrin approach is that it does not involve encapsulation of a protein drug inside PLGA, avoiding the exposure of a protein drug to the processes involved in the o/w/o or s/o/w double emulsion methods. This is expected to maintain the bioefficacy of the loaded protein better than other systems. Although the NP–Fibrin system requires a functional component, such as heparin, that binds a protein drug of interest, it can serve well as a general platform for long-term delivery of various protein drugs.

References

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