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Cover story

Biodegradable thermosensitive polymer gel for sustained BMP-2 delivery

Bone morphogenetic protein-2 (BMP-2), which belongs to the transforming growth factor-beta superfamily, is known to induce differentiation of bone regenerative cells. The BMPs provide great osteogenic abilities, such as affecting recruitment, differentiation, and proliferation of osteoprogenitor cells [1]. Effective delivery of BMPs can be an alternative therapy to transplantation of autogenic or allogeneic bone grafts in treatment of bone healing. An ideal BMP delivery system is expected to function as a physical scaffold for cell infiltration as well as sustained BMP delivery for bone regeneration. Increased retention time of BMPs at the administered site is also required for bone-regenerative cells to migrate to the area of injury, proliferate and differentiate [2]. To this end, an absorbable collagen sponge (ACS, INFUSE®) incorporating BMP-2 was introduced for achieving open tibial fracture healing in human patients [3]. Other implantable materials, including tricalcium phosphate, demineralized bone matrix, and synthetic polymers, have been used with BMP-2 as a bone regeneration-promoting scaffold or as a local BMP-2 delivery carrier. Most of these implantable materials with BMP-2, however, have disadvantages, such as requiring of surgical procedures involving additional soft-tissue exposure, using high doses of BMP-2, uncontrollable BMP-2 release, and difficulties placing them at the exact location. These problems are aggravated by the short half-life of minutes and poor stability of BMP-2. In this issue, Dr. Soo-Chang Song and his colleagues developed an injectable and thermosensitive and biodegradable polymeric nanoparticle hydrogel system that can overcome those limitations [4].

The system by the Song group is based on the poly(phosphazene) polymer substituted with hydrophobic isoleucine ethyl ester and hydrophilic poly(ethylene glycol) for amphiphilicity and thermosensitive sol–gel transition property [5] and with carboxylic acid moiety for interacting with the positively charged BMP-2. These dual interacting polymeric nanoparticles (D-NPs) form compact nanocomplexes in the presence of BMP-2, keeping the protein inside the hydrogel network. The thermosensitive transformation of nanocomplex solution to hydrogel at the body temperature allows injection into the body, suppression of the initial burst release, extended retention at the injected site, continuous stimulation of bone generation, and efficient generation of new bone. D-NPs were superior to the control polymer without carboxylic acid groups the longer duration of BMP-2 release (21 days vs. 10 days), and 14–50% higher bone regeneration ability in ectopic and orthotopic bone generation tests with no sign of inflammatory responses at the injection sites during the animal experiments. The thermosensitive and biodegradable hydrogel system by Dr. Song's team could provide clinical benefits for its non-surgical administration with increased safety. The system can also be used as a platform technology for protein delivery because proteins have hydrophobic domains and individual isoelectric point at physiological condition of pH 7.4, which could interact with the dual interacting polymeric nanoparticle.

For more than a decade, a very large number of nanoparticle systems have been developed mainly for the tumor-targeted drug delivery. But a real potential of nanoparticle systems as a drug delivery vehicle may be found in other applications. As shown by the Song group, nanoparticle hydrogel systems can be effectively used in localized, sustained delivery of BMP-2 with good outcomes. Current nanotechnology allows manipulation of nanoparticle properties as desired, and this ability can be used wisely by choosing the right applications. Until the time when scientists can figure out how to control biodistribution of nanoparticles after intravenous injection, the sensible use of nanoparticles may reside in localized delivery.

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