NIDCR National Institute of Dental and Craniofacial Research

Periodontal Disease: Early Progress Reported in Tissue Engineering

For Immediate Release:
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Scientists have long known that platelet-derived growth factor (PDGF) has the potential to help regenerate the lost bone and soft tissue that occurs with advanced periodontal, or gum, disease. The problem always has been finding a way to administer PDGF that prevents scissor-like enzymes in the wound from snipping the growth factor to pieces and degrading it before complete regeneration can occur.

Now, as a potential solution to this problem, a team of researchers at the University of Michigan reports the first success at using gene therapy to administer PDGF to the wound in rats. According to the article, published in the April issue of the journal *Molecular Therapy*, the scientists inserted a copy of the PDGF gene into the much studied adenovirus, which transported the gene past the destructive enzymes and into cells surrounding the lesion. Once there, the scientists reported the gene produced increased amounts of PDGF protein for up to three weeks, while prompting the regeneration of bone, formation of the tooth-supporting periodontal ligaments, and enhanced deposition of root-covering cementum.

Stressing their strategy still faces many scientific hurdles, the authors say their experiments mark an important first step in developing PDGF gene therapy for the treatment of periodontal disease, which affects an estimated 200 million Americans to varying degrees. "This really is a proof-of-concept study, meaning that it is not yet ready for clinical applications, but we have shown that PDGF gene therapy is possible. There are still questions that we hope to answer with further refinement of the therapy," said Dr. William V. Giannobile, the senior author on the study and a scientist at the University of Michigan. The work was supported by the NIH’s National Institute of Dental and Craniofacial Research.

This month’s paper builds on the group’s previous successes in the laboratory at introducing the PDGF gene into cells. Because cells normally do not take up DNA by themselves, scientists often rely on viruses, which can bind to and enter cells, bringing their own or a manufactured gene with them. Here, the scientists packaged the PDGF gene in an adenovirus and used it as a treatment in a periodontal disease model. In this infectious disease the body’s immune response not only affects the invading oral bacteria, but also the healthy gum and bone tissue. As a result, large gaps develop around the teeth that can eventually lead to tooth loss.

To simulate these periodontal lesions in their animal study, the scientists created large holes in the jaws of anaesthetized rats. The PDGF-adenovirus, mixed with collagen, a major supportive tissue in the body, was then delivered to the wounds.

Two weeks after the surgical procedure, the PDGF-treated rats showed more bone and blood vessel formation than the control rats. These are indications of the growth stimulating effect of PDGF, which attracts other cells to come to the damaged site and start the reparations.

The scientists said collagen was used to immobilize the virus and prevent it from spreading and acting beyond the wound elsewhere in the body. They demonstrated the virus did stay localized by using an adenovirus with a fluorescent gene, luciferase, which only lit up close to the wound tissue. Still, after only a few weeks much of the fluorescent light had decreased, indicating that the gene expression was limited.

The use of adenoviruses might explain this phenomenon. An important aspect with adenovirus is that it triggers a body’s immune response to eliminate the virus, because it is seen as an intruder. This makes the protein production only short-lived, but the scientists believe that to be a good thing here. "Wound repair occurs in a controlled fashion for a short period of time, so PDGF gene delivery with adenovirus works to our advantage in this case. Also, we would not want to deliver a growth stimulating molecule permanently, because it could lead to tissue overgrowth," explained Giannobile.

Current treatments for periodontal disease only focus on stopping disease progression, but the damaged tissue is lost forever. The ultimate goal of Giannobile’s and other research groups is to regenerate all destroyed periodontal tissues. In the tissue engineering process PDGF is a helpful player to create some of that new tissue. "For now, we have shown that adequate delivery of PDGF is a move in the right direction."

The next step in PDGF gene therapy will be to test the concept in larger animal models. According to Giannobile: "It is time to study more complex disease situations than the rat model, which mimic the human situation better."

Collaborating with Dr. Giannobile were Drs. Qiming Jin, Orasa Anusaksathien, Sarah A. Webb, and Marie A. Printz. The study is titled "Engineering of Tooth-Supporting Structures by Delivery of PDGF Gene Therapy Vectors" and it was published in the journal *Molecular Therapy* in April, 2004.