Collagen-targeted growth factors for bone healing

Rick Visser [1, 2], Pilar M. Arrabal [2, 1], Leonor Santos-Ruiz [2, 1], Jose Becerra [1, 2], Manuel Cifuentes [1, 2]

1. Dept. of Cell Biology, Genetics and Physiology, Faculty of Science, University of Málaga. Campus de Teatinos, s/n. 29071 Málaga. Spain.
1. CIBER-BBN, Dept. of Cell Biology, Genetics and Physiology, Faculty of Science, University of Málaga. Campus de Teatinos, s/n. 29071 Málaga. Spain.

visser@uma.es

Reparation of bone defects and fractures is a major clinical and economic concern, being millions of bone grafts performed each year in the United States and the EU. Despite the acceptable bone induction properties of autologous bone grafts, the high morbidity of these approaches and limited amount of material that can be obtained from the donors is forcing the development of bone tissue engineering products for the restoration of damaged or lost bone. This search for alternatives led to the approval by the FDA of an absorbable collagen carrier combined with recombinant human bone morphogenetic protein-2 (rhBMP-2) for the treatment of certain bone diseases and fractures (INFUSE®, Medtronic, Minneapolis, MN, USA).

Osteoinductive growth factors have to be used in combination with a suitable osteoconductive carrier to retain them at the wound site, and permitting a slow release into the extracellular milieu. Although none of the today available carriers can be considered ideal, collagen is one of the most frequently used in experimental studies because of its versatility, high biocompatibility and low immunogenicity. Nevertheless, since most growth factors have a low natural affinity to collagen, these approaches require the use of very high doses of these osteoinductives, increasing the costs and decreasing the safety of these treatments.

In order to design cheaper and more safe delivery systems, we have developed a modified rhBMP-2 with an additional collagen-binding domain (CBD) derived from the von Willebrand factor. This rhBMP2-CBD demonstrated to have an improved affinity to absorbable collagen sponges (ACS) and the ability to induce ectopic bone formation at lower doses than native rhBMP-2 [1].

Since osteogenesis is a multimodal process, with many different growth factors and signaling routes involved, we are currently dedicated to the design of more complex and efficient alternatives to this system by including collagen-targeted angiogenic growth factors (rhFGF-2 [2]) and synthetic osteoinductive peptides with the aim of obtaining an “activated” ACS to improve osteogenesis in vivo.

References

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[2] Andrades JA, Wu LT, Hall FL, Nimni ME, Becerra J. Growth Factors. 2001;18(4):261-75.

Figures

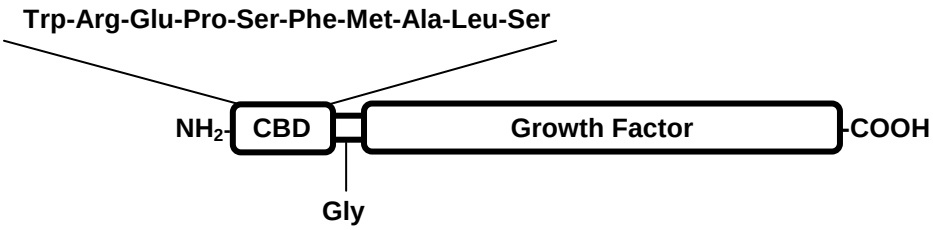

Fig. 1. Schematic representation of a collagen-targeted fusion protein construct.