3.1.1.2 Mechanism of BMP-7 Induced Bone Formation

Numerous studies have evaluated the efficacy of OP-1 in conjunction with collagen for local repair and regeneration of bone defects. These include the long bones, craniofacial bones, and spinal column.[18,19,20] OP-1 in combination with collagen is an efficacious bone graft substitute in a variety of animal species, including rat, rabbit, dog, sheep, goat, monkey, and baboon.

The rat SC bone formation assay is a standard method used to evaluate the osteoinductive activity of BMPs. Implantation of purified recombinant BMPs with bone collagen matrix in SC sites induces a sequence of cellular events that leads to the formation of new bone complete with bone marrow elements. Only osteoinductive BMPs such as OP-1 display this activity.[3] The first step in the bone induction process involves recruitment of nearby mesenchymal stem cells into the collagen matrix. OP-1 first stimulates the stem cells populating the matrix to proliferate and then triggers their differentiation into chondrocytes in 5 to 7 days. Cartilage is formed first, but after invasion by capillaries the chondrocytes hypertrophy, become calcified, and osteoblasts appear at the administration site. Newly formed bone is present 9 to 12 days following implantation. Subsequently, the bone is remodeled extensively and becomes occupied by ossicles filled with bone marrow elements at 14 to 21 days. This cellular process is referred to as "endochondral bone formation." OP-1 can also induce bone formation through "intramembranous bone formation" where OP-1 triggers mesenchymal cells to differentiate directly into osteoblasts and thus bypass the cartilage stage.

OP-1 initiates a cascade of biological events during bone formation. The resulting processes involve interactions with the mesenchymal cells including chemotaxis, proliferation, and differentiation into bone and/or cartilage cells. The subsequent steps appear to rely on a range of contributing factors, including other BMPs. Recent studies demonstrate that OP-1 induces the expression of numerous growth factors and multiple members of the BMP family (including autoinduction), during the bone induction process.[21,22] These factors guide the bone formation process to completion. In vitro studies have shown that OP-1 perpetuates mechanisms involved in bone formation, including: a) promotion of chondrocyte maturation (extracellular matrix component production) in normal articular chondrocytes; b) enhancement of osteoblastic characteristics (alkaline phosphate production) of normal osteoblast cells; and c) induction of the differentiation of osteoclasts involved in the bone remodeling process. The end result of this differentiation cascade is the production of weight-bearing bone with fully functional bone marrow elements.[3]

Numerous animal studies have been performed that support the efficacy of OP-1® Putty for use in the spine.[18,23] These studies were performed in multiple models and support the feasibility of OP-1® Putty as an acceptable alternative to autograft. Specifically, posterolateral fusion utilizing OP-1® Putty is effective in rabbit, dog, and sheep models.

For purposes of clarity, we will refer to the bone that forms at a site of implantation or injection of OP-1 as "heterotopic bone." We will refer to bone that potentially forms away from the site of implantation or injection of OP-1 as "ectopic bone."

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