Bone growth into bone damaged sites is generally believed to develop through a regenerative process that involves autologous bone grafting. However, even in the absence of bone regeneration, biomimetic medical devices have been developed to provide a structural alternative to bone grafting. In recent years, the development of these devices has demonstrated that bone can be induced to regenerate through chaotic molecular signaling pathways. This article explores the concept of bone induction through chaos, focusing on the role of biomaterials and the chaotic molecular signaling pathways involved.

**REGENERATION THROUGH CHAOS**

Ever since Hippocrates (400BC) reported on the unique phenomenon of bone healing without apparent scarring, biological scientists have been trying to unravel the unique and primary controlling mechanism by which bone heals itself with the principle of replicating and controlling its regeneration.

For centuries surgeons have tried to restore large bony defects with little or no success, until the publication of bone regeneration studies by Schede (in Senn, 1889), who utilized blood coagulation as a method to regenerate osteogenic defects. Senn (1889) then developed a medical treatment for osteogenic repair based on Schede’s blood coagulation principle in canine models, in which decalcified bone matrix was used as a means to repair bone defects. Despite these discoveries, bone grafting, a treatment still utilized for regenerative repair, is no longer restricted to autologous bone. The authors of this article have developed and tested the efficacy of other regenerative treatment options, including those based on autologous tissue and biological signaling stimuli.

**Bone Morphogenetic Proteins (BMPs)**

Bone morphogenetic proteins (BMPs) were first discovered by Urist (1965) and later extracted and cloned by Wozney et al. (1988). BMPs are a family of proteins that are involved in the regulation of bone formation and regeneration. They have been shown to induce bone formation when administered to porous devices, which are commonly used in bone grafting procedures. BMPs are able to induce bone formation by activating osteogenic cells, which then differentiate into bone-forming cells.

**Chaotic Molecular Signaling Pathways**

The study of chaotic molecular signaling pathways is an emerging field in bone regeneration research. Chaotic signaling pathways are characterized by their unpredictable, non-linear behavior and are often associated with bone formation. The authors of this article have explored the role of chaotic signaling pathways in bone regeneration, and have shown that these pathways can be harnessed to enhance bone regeneration.

**Experimental Evidence**

The authors have conducted experiments using chaotic signaling pathways to enhance bone regeneration. One experiment involved the use of a porous collagen scaffold implanted into the calvarial bone defects of New Zealand White rabbits. The scaffold was loaded with BMPs and a growth factor, and the results showed a significant increase in bone regeneration compared to the control group.

**Conclusion**

The authors conclude that chaotic molecular signaling pathways are a promising approach to enhancing bone regeneration. Further research is needed to fully understand the mechanisms involved in chaotic signaling pathways and to develop new treatments for bone regeneration.

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**FIGURE 1**

In chaos there is order. Two calcium phosphate macroporous devices A and B, loaded with two bone inducing morphogens each, implanted into heterotopic sites of non-human primates Papio Ursinus. Both of the devices are in close proximity to each other. Bone formation (red arrows) occurs within each device, together with some cartilage formation (blue arrow) and bone marrow development (brown arrow), in a potential tractional field between the two implanted macroporous devices (magnification 2x).
which zoledronic acid a bisphosphonate derivative, prevented the active binding of osteoclasts to the macroporous devices (Ripamonti et al., 2010), demonstrated the loss of the expression of either OP-1 or TGF-β, morphogens and their subsequent signaling protein secretion. This indicates that both morphogens must be expressed in order to facilitate successful bone formation.

Thus both osteoclast attachment (driven by the chemical composition and physical characteristics of the scaffold) and the subsequent expression of these two morphogens are required to stimulate proper bone formation by autoinduction. Furthermore this suggests that the primordial initiating mechanism is not comprised of a singular all-controlling pathway, but of a mixture of more than one signal (Figure 1). With this knowledge the author is of the opinion that all future bone induction research should focus on finding and analyzing which mixtures of stimulatory, regulatory/inhibitory morphogens coupled with other non-biological signaling mechanisms work best together to increase the rate and the deposition of bone. After all in chaos is there not order? (Lorenz, 1963).

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