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NARRATIVE REVIEW

Bone grafts: Characteristics, properties, indications, contraindications for predictable bone regeneration - Part 1.

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Keywords: Bone graft; bone substitutes; bone regeneration; guided bone regeneration; bone properties; osteogenesis; osteoinduction; osteoconduction; osteopromotion; osteotransduction.

ABSTRACT

Objective: To perform a systematic literature search to summarize the characteristics, indications and contraindications as well as the requirements to obtain a predictable bone regeneration.
Materials and methods: A systematic search was carried out in databases such as GOOGLE SCHOLAR, LILACs, PUBMED between 2002 and 2024. In addition, a manual search was performed according to the authors' criteria. The articles that met the inclusion and exclusion criteria related to the objective of the present review were selected.
Results: The systematic search yielded 350 articles of which 42 were included in the present review. Bone graft concepts, indications and contraindications as well as clinical requirements for predictable guided bone regeneration were extracted.
Conclusion: Autografts remain the gold standard in terms of regeneration of neoformed bone tissue. Allografts and xenografts have also shown predictable results overcoming the limitation of autografts in terms of availability and lower morbidity.

CLINICAL RELEVANCE

Knowledge of bone substitutes in terms of their indications and contraindications is fundamental to obtain predictable bone regeneration results for the clinician. The diagnosis of the bone defect to be regenerated, as well as the characteristics of the gingiva, are aspects to be taken into account within the surgical principles. Knowing the properties of each bone substitute will allow the clinician to advise the patient in the selection of the best biomaterial to solve his clinical situation in a predictable way and with long-term results.

INTRODUCTION

Definition of bone grafts

A graft is defined as a biomaterial designed to act interfascially with biological systems in order to evaluate, treat, augment or replace some tissue, organ or function of the body.[1, 2]

The materials used in bone regeneration can be of human, animal or synthetic origin; the latter can be modified or transformed by various processing methods to behave as bone substitutes; therefore, we can define bone grafts as those materials of biological or synthetic origin that are used to promote a response based on osteogenic, osteoinductive, osteoconductive, osteopromoting and osteotransduction properties that characterize the patient's native bone tissue, in order to form bone (Figure 1A, B, C).[3]

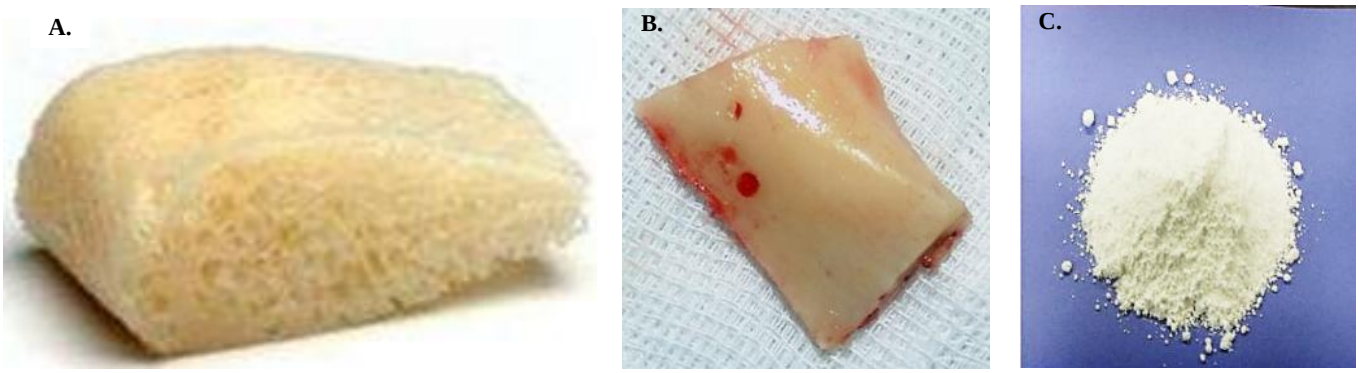

Figure 1. Types of bone grafts. A) Allograft B) Autograft C) Tricalcium phosphate (Biocomposite).

The use and selection of bone substitutes by the clinician is relevant in terms of predictable outcomes for the patient. Several factors influence this point which involve local and systemic conditions of the patient as well as the knowledge of the properties, indications and contraindications of bone grafts. The present literature review focuses on the second aspect and aims to clarify to the clinician the properties, indications and contraindications of bone substitutes for an easy and accurate selection in each clinical situation presented by the patient.

MATERIALS AND METHODS

Three systematic search strategies were carried out in the following databases: Google Scholar, LILACs, PubMed, which are described in Table 1. A manual search according to the authors' criteria was also performed according to the objective of the present review.

A manual search was performed looking for repeated references in the articles found to be excluded. The following inclusion and exclusion criteria were applied.

Inclusion criteria

Articles published between 2002 and 2024 as controlled clinical trial, systematic review of literature, experimental study in humans, with histomorphometric evaluation, description of properties of bone grafts used, use of autografts, allografts, xenografts and alloplastics such as calcium phosphate.

Exclusion criteria

Narrative review articles, case reports, experimental animal studies.

Table 1. Search strategy applied in the databases.

Databases	Search strategy	Search results
Google scholar	Bone graftrs AND bone substitutes AND bonegrafts properties AND bone indications AND histomorphometry AND periodontal defects	3710

LILACs	(bone grafts) OR (osteoinduction) OR (osteogenesis) OR (osteoconduction) AND NOT (membranes) AND (periodontal defect) AND mj:("Regeneración Tisular Guiada Periodontal" OR "Regeneración Ósea") AND type_of_study:("clinical_trials") AND la:("en") AND (year_cluster:[2015 TO 2025]) AND instance:"lilacsplus"	5
PubMed	((((bone grafting[MeSH Terms]) AND (alveolar resorption[MeSH Terms])) AND (osteogenesis[MeSH Terms])) AND (bone regeneration[MeSH Terms])) AND (guided periodontal tissue regeneration[MeSH Terms])	12

After applying the inclusion and exclusion criteria, 42 articles were selected for full reading (Figure 2).

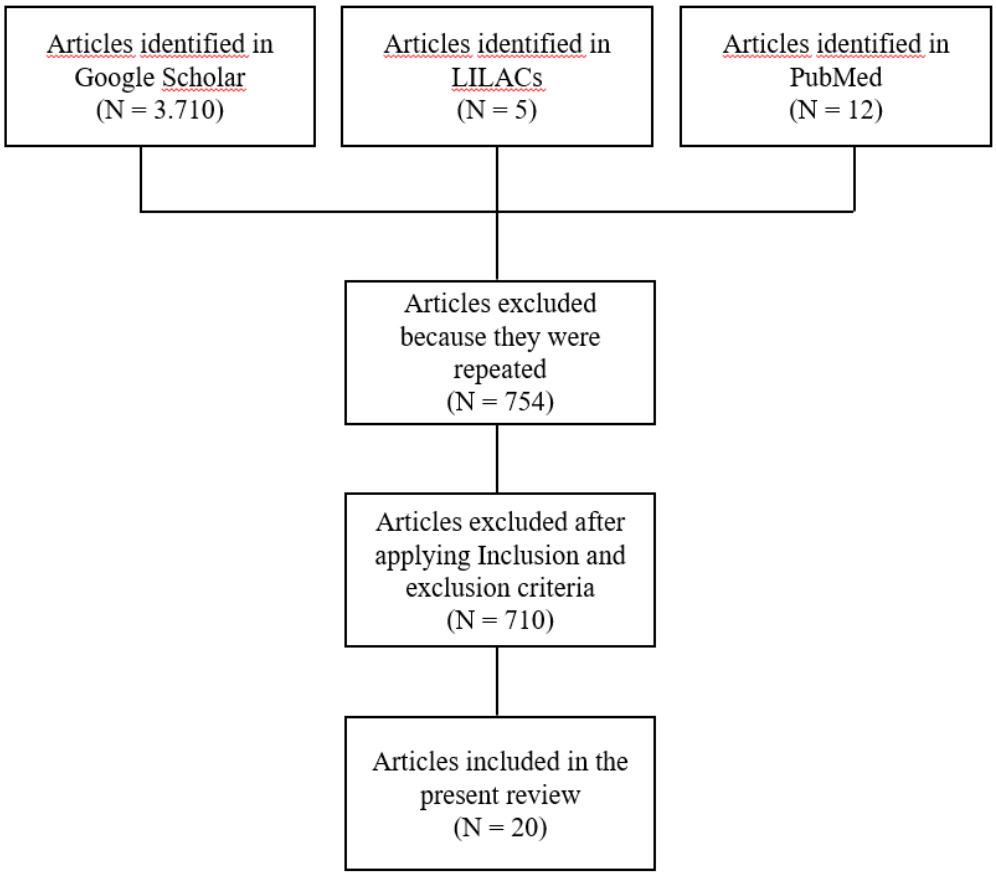

Figure 2. Flow diagram summarizing the search strategy, results and application of inclusion and exclusion criteria for the selection of articles for this review.

RESULTS

Of the 20 articles selected, the authors extracted by topic those studies that responded to the definition of the characteristics, indications and properties of bone grafts, as well as the requirements for bone formation, which are described below.

Characteristics of bone grafts

1. *Biocompatibility:* A characteristic of bone grafts is their ability to interact within a hostile biological environment induced by the host's immune system, therefore, it is necessary to develop minimal or no activation of the immune system, thus we speak of a characteristic known as “Biocompatibility of the material”.
2. It should not be toxic by itself or by the products produced by its degradation.
3. It should not be carcinogenic in the short or long term, either by itself or by its degradation products.
4. It should not be hemodynamically incompatible with the environment in which it is implanted.

General indications for bone grafting

Bone defects in oral and craniofacial tissues caused by trauma, tumors, infections, justify the use of both grafts and biocompatible bone substitutes. Additionally, one of the most commonly used methods for the reconstruction of infraosseous defects is the combination of implanting bone grafts or biomaterials into the debrided bone lesion in order to regenerate the lost periodontal tissues.[4]

Additionally, a clinical reason for using bone grafts and bone substitutes is that they stimulate the regeneration of the attachment apparatus (including the formation of alveolar bone and new connective tissue attachment), because some of these materials not only possess osteoforming cells but also act as a scaffold for bone support and formation; additionally, bone grafts release osteo-inducing substances found within their matrix, allowing them to carry out bone formation.[4,5]

Therefore, they are also indicated to increase the thickness and height of the alveolar ridge in sites where one or more dental implants are going to be installed, as well as in atrophied rims (Seibert I, II and III) when a rehabilitation with fixed prosthesis is planned. Finally, they are indicated for the reconstruction of bone tissue after bone loss caused by trauma (traffic accident, bullet impact, among others).

Relative contraindications for bone grafts

Patients with uncontrolled diabetes

Healing in patients with uncontrolled diabetes is much slower and is accompanied by a decrease in bone mass, as poor glycemic control leads to increased bone resorption and bone loss.[6] This phenomenon can be explained in patients whose levels of Streptozotocin (STZ) are elevated in the pancreas. STZ in the pancreas inhibits superoxide dismutase which is responsible for scavenging free radicals; when free radicals are not scavenged, it results in an accumulation of free radicals and local destruction of islet beta cells, which are responsible for the production of insulin, necessary for glycogen scavenging. Because insulin release is reduced, concomitantly collagen production decreases. Additionally, the slow rate of bone remodeling is due to an inactivation of osteoclasts followed by decreased osteoclastic activity, as well as decreased protein synthesis and decreased phosphatase activity in osteoclasts.[7]

Smoking patients (due to Nicotine)

Nicotine affects the oxygenation of bone tissue thus causing low oxygen tension in the grafted area, predisposing to fibrous tissue scarring, increasing healing time.[8]

Moreover, other relative contraindications to the use of a bone substitute are summarized in Table 2.

Table 2. Relative contraindications to the use of a bone substitute.

- Skeletally immature patients
- Patients with severe vascular or neurological disease
- Women during the period of pregnancy or one year prior to becoming pregnant
- Patients with active or chronic infection at the site to be regenerated
- Patients with hypercalcemia
- Patients with inflammatory bone disease such as osteomyelitis.
- Patients with severe renal dysfunction
- Patients with history of Pott's disease
- Uncooperative patients who are unable to follow postoperative instructions, including individuals who abuse drugs and/or alcohol.
- Patients with known hypersensitivity to Recombinant Human Bone Morphogenetic Protein-2.
- Patients with known hypersensitivity to bovine collagen Type I.
- Some grafts should not be implanted immediately after a tumor that has not been removed or immediately after its removal.

Properties of bone grafts

Bone grafts must comply with certain properties to allow bone formation. Among the properties of bone grafts and bone substitutes (Biomaterials) are osteogenesis, osteoinduction, osteoconduction, osteopromotion and osteotransduction.

Osteogenesis

An osteogenic material can be defined as one that contains living cells capable of differentiating into bone-forming cells, forming bone matrix, blood vessels to give rise to new tissues and replace lost tissues.[9]

The process of osteogenesis can be observed during the healing of an alveolus as follows (Figure 3A, 3B):

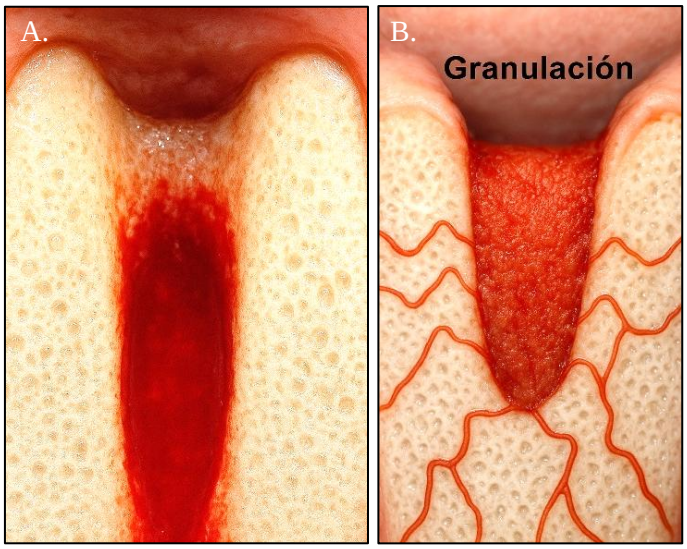

Figure 3. A) Alveolus where the bone regeneration process will take place. B) The bone, being highly vascularized, fills the alveolus with blood to form the blood clot in a granulation phase. Figure taken and enhanced with AI.

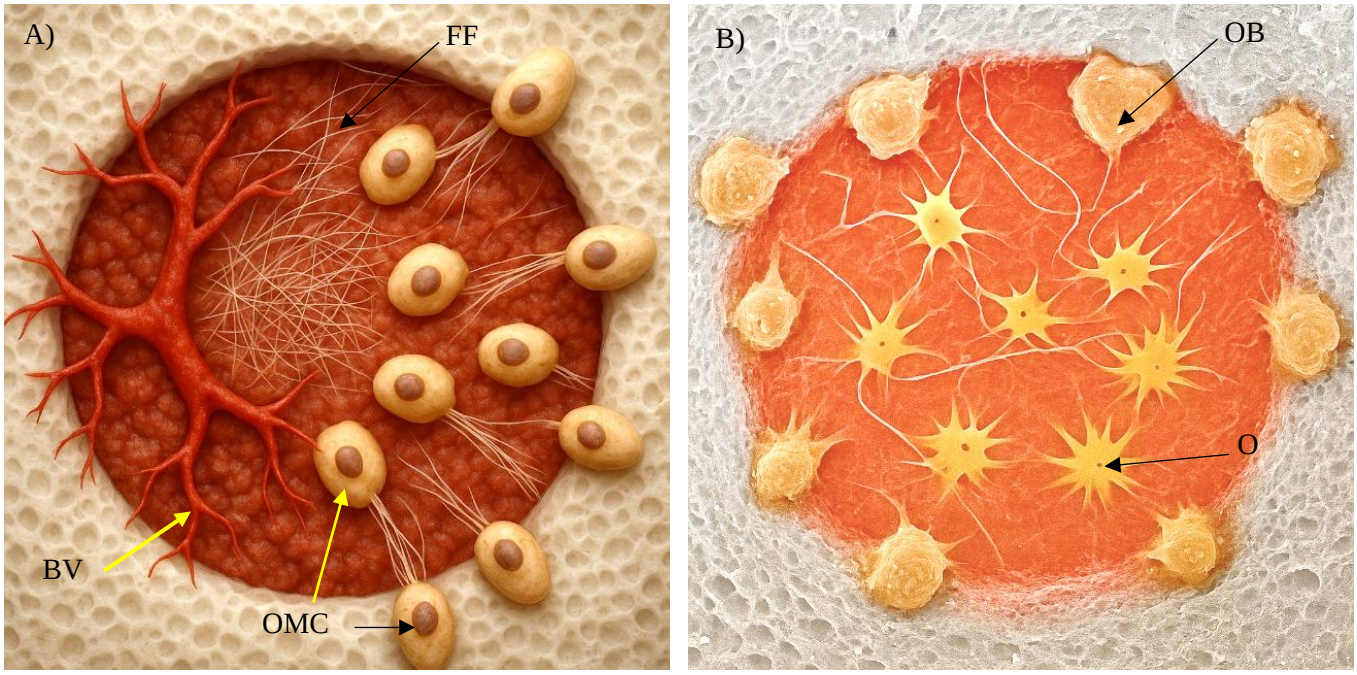

Figure 4. Coronal view of the alveolus where osteogenesis occurs. Blood vessels (BV) in red and fibrin fibers (FF) are observed around the entire surgical alveolus. A) Osteogenesis shows populations of osteoprogenitor mesenchymal cells (OMC) with the potential to proliferate and differentiate into osteoblasts found in the bone marrow, endosteum and periosteum of the patient's native bone. B) The osteoprogenitor mesenchymal cells migrate to the site to be regenerated and change shape becoming osteoblasts (OB), which are cells in charge of secreting extracellular organic matrix and in turn control its mineralization when differentiate in osteocytes (O).

The differentiation and development of osteoblasts from osteoprogenitor cells occurs thanks to the release of growth factors by cells found at the site to be regenerated, such as platelets, leukocytes, fibroblasts, macrophages, endothelial cells, among others. Growth factors are biological mediators that regulate important cellular events during tissue repair; when growth factors bind to their specific receptors on the cell surface, they enhance the ability of cells to regenerate bone tissue, increase their ability to perform chemotaxis, cell differentiation and proliferation. Some growth factors involved in the osteoblast differentiation process are bone morphogenetic proteins (BMP), insulin growth factor (IGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) among others.

Osteoblasts, as well as osteoprogenitor mesenchymal cells, depend mainly on a phenomenon known as angiogenesis (formation of new blood vessels). Additionally, blood vessels can change their distribution and structure by establishing new connections with other blood vessels within the site where healing is occurring or as a result of bone matrix synthesis.

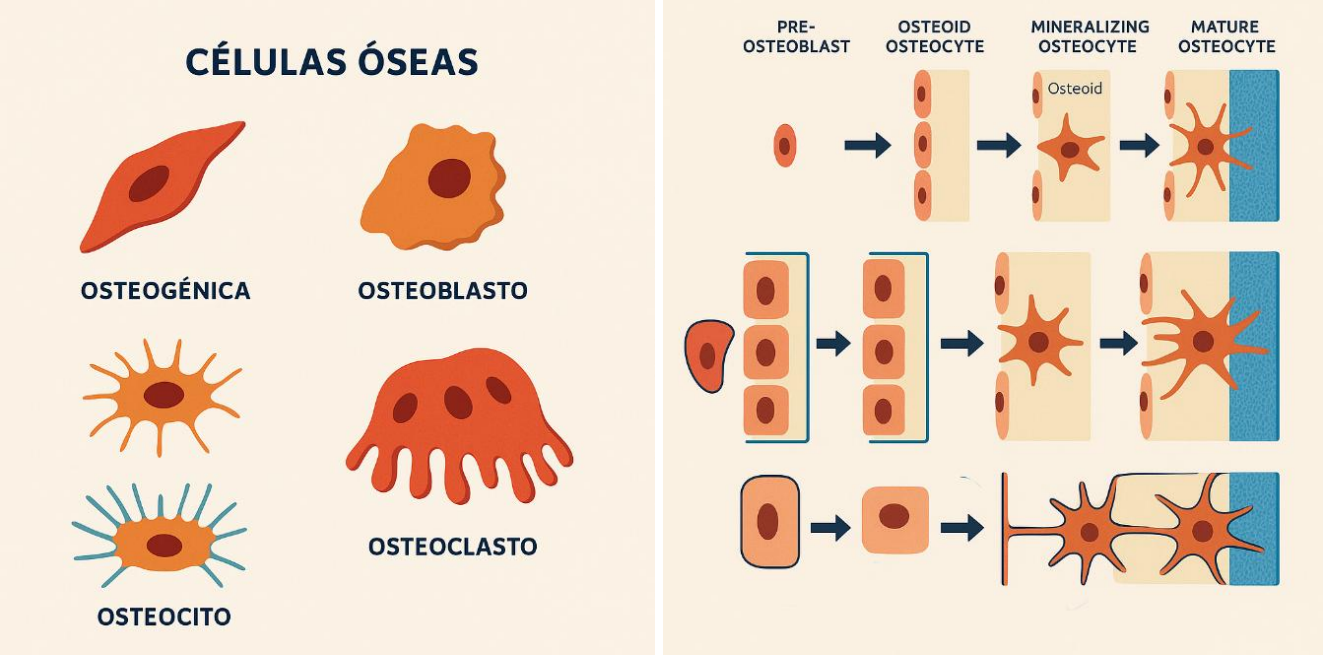

Figure 5. A) Bone cells involved in bone regeneration and remodeling process. B) As osteogenesis proceeds, some osteoblasts become trapped within their own mineralized bone matrix, thus becoming osteocytes. Osteocytes are stellate-shaped cells which are considered as the main osteoprogenitor cell, since they regulate calcium homeostasis, maintain a connection with other bone cells by means of canaliculi that go through the bone matrix and, additionally, these cells are confined to the bone surface to maintain their integrity by means of a continuous synthesis of bone matrix, which is occurring in the same direction where the blood vessels are directed.

In conclusion, osteogenesis involves the healing process where a series of biological processes occur aimed at reestablishing the original form and function of the tissue that has been lost due to different causes (trauma, infection, tumor, among others).

Osteoinduction

Osteoinductive materials provide the biological stimulus that induces the phenotypic differentiation of mesenchymal cells into bone-forming cells. In other words, it is bone healing at the expense of a process in which cells are “coaxed” to synthesize new bone, and involves a phenotypic differentiation of mesenchymal cells into bone-forming cells.[11] In turn, Albrektsson & Johansson (2001) define osteoinduction as the stimulation of undifferentiated, pluripotential mesenchymal cells to differentiate into osteo-forming cells.[12]

Importance of Osteoinduction in Bone Healing

In addition to osteoblasts, osteocytes and osteoclasts, bone tissue has undifferentiated mesenchymal cells that play an important role in bone healing. These undifferentiated cells can be recruited and induced to differentiate into osteoforming cells. Upon stimulation by an osteoinductive agent, undifferentiated mesenchymal cells can be transformed into preosteoblasts, a process known as bone induction or osteoinduction (Figure 6A).

The first experiments on osteoinduction were performed by Urist (1965) who used freeze-dried demineralized bone taken from both laboratory animals and humans in order to use it as an osteoinductive agent to promote bone regeneration in bone defects. Ursit implanted the freeze-dried demineralized bone samples, from each specimen and patient, in bone defects at the ulnar bone level in 10 rabbits, in the lumbar vertebra of 3 dogs, as well as in bone defects in 21 humans with skeletal disorder (author does not specify the type of disorder).[13]

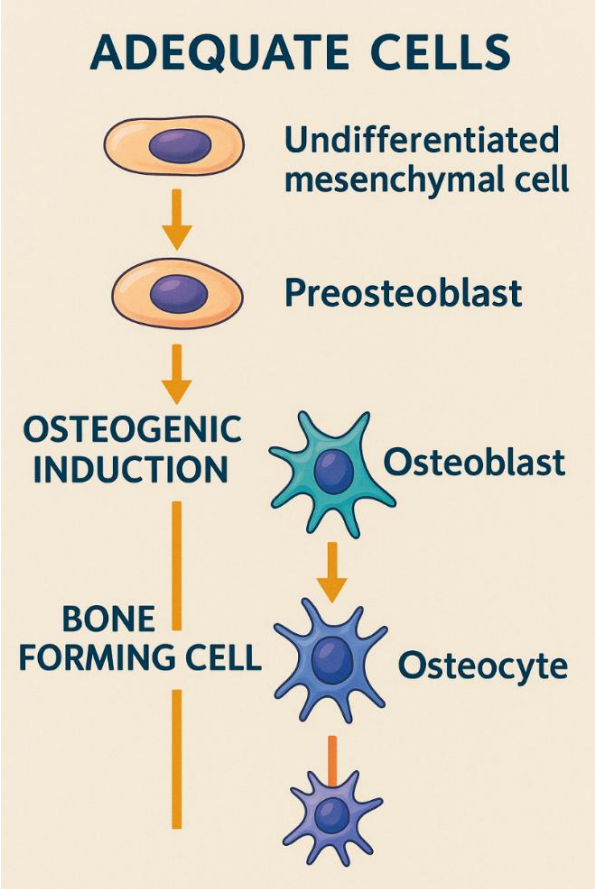

Figure 6. At the time of injury, both undifferentiated cells and differentiated bone cells are involved. Undifferentiated cells are induced (osteoinduction) to differentiate into preosteoblasts. Figure taken from Albrektsson & Johansson (2001)[12] and edited and enhanced with AI.

Urist's findings revealed a chemotaxis of histiocytes (inducer cell) to the area where the graft bone matrix was implanted within the first 3 weeks of healing. Additionally, these histiocytes began a process of matrix resorption, released chemical agents, stimulated capillaries and perivascular connective tissue to create long channels that were occupied by their descendant cells. "*When a histiocyte (inducer cell) and a perivascular connective tissue cell (induction-responsive cell) interact and divide, such cell differentiation occurs through a phenomenon known as Autoinduction, the goal of which is to produce an osteoprogenitor cell or a chondroprogenitor cell*" (Urist, 1965).[13]

Urist (1965) proposed the existence of "tissue-specific factors" as responsible not only for guiding undifferentiated cells, but also for controlling their migration, aggregation, translocation and regrouping. These specific factors had the ability to favor cell-cell adhesion as well as the transmission of an inductive stimulus, explaining why histiocytes with a special predisposition towards osteogenesis were found adhering to demineralized lyophilized bone. In addition, he described how a group of proliferating cells induced the differentiation of perivascular connective tissue cells into osteoprogenitor cells and subsequently into osteoblasts.

Subsequently, Urist et al (1997) succeeded in isolating a glycoprotein called Bone Morphogenetic Protein (BMP) as an osteoinductive agent. BMP belongs to a family of growth factors called, transforming growth factor-β (TGF- β). BMPs are naturally released in response to trauma or when bone remodeling occurs.[14]

This is why osteoinduction, the process of recruitment of osteoprogenitor mesenchymal cells and their stimulation to differentiate into pre-osteoblasts, is a basic biological mechanism that occurs regularly in fracture healing, bone defects, and implant biointegration.[12]

According to Frost's theory, when an injury occurs in soft tissues and bone tissue, a repair process is initiated through the sensitization of different cell types and, simultaneously, there is a release of local biochemical and biophysical messengers known as growth factors, which promote a cellular response, guide cellular differentiation and organization to obtain adequate healing (Figure 7). This initial phase of healing necessarily involves the presence of Osteoinduction, a process that begins immediately after the injury and is very active during the first week of healing.[12]

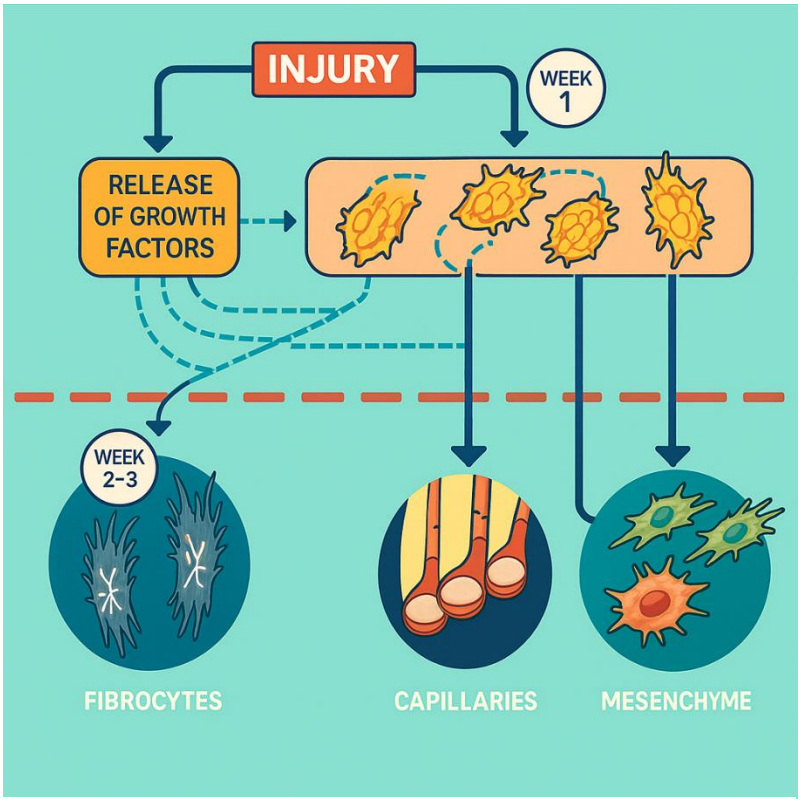

Figure 7. According to Frost's theory, injury elicits a healing response through the release of growth factors and sensitization of cells, which differentiate to give rise to the injured tissues. Figure taken from Albrektsson & Johansson (2001)[12] and edited and enhanced with AI.

Gene therapy for Osteoinduction

More than a decade ago, gene therapy has been considered not only to treat defects in tendons, ligaments and cartilage but also to induce bone formation and improve healing in bone defects caused by trauma, tumors, osteonecrosis, infections or congenital conditions among others.

Gene therapy is the process of transferring genetic information into a group of cells. When a gene is properly transferred to the target cell (the cell we specifically want to treat), this cell synthesizes the protein encoded by the gene; the duration of the synthesis of this protein depends on the techniques used to release the gene from the cell.[15]

The duration of the required protein production and the anatomical location where the protein is to be released determines the type of gene therapy to be employed, as there are many therapeutic options available. Gene therapy can therefore be regional or systemic and can be performed by an in vivo technique (when the gene can be introduced directly to a specific anatomical site) or by an ex vivo technique (when specific cells can be taken from the patient to be cultured and genetically manipulated in a laboratory, and then reimplanted into the patient's tissue to be treated).[15]

Gene therapy performed by the ex vivo technique can be used to enhance the osteoinductive effect when bone marrow cells, myoblasts, osteoblasts, fibroblasts and mesenchymal stem cells are infected with an osteoinductive gene. Additionally, this technique has the advantage of being safer and allows obtaining more consistent results because the viral particles or DNA complexes are injected only into cells that express the protein of interest at high levels; however, it has the disadvantage of being a more complex and time-consuming procedure.

Another technique used in gene therapy is the use of vectors. Vectors are agents that enhance the entry and expression of exogenous DNA into the target cell, allowing gene expression to be initiated and resulting in the expression of the desired protein. Vectors can be viral or non-viral. Viruses are efficient vectors since DNA expression and delivery are essential for their normal life cycle.

In this vein, the use of bone marrow cells for gene expression has many advantages since these cells can be easily harvested, cultured, possess an inherent osteogenic capacity and are able to respond to the morphogenetic proteins (BMPs) they have been designed to secrete. For this reason, ex vivo gene transfer into bone marrow cells using a viral vector (adenovirus) containing complementary BMP-2 has been used in animal studies to improve bone healing in critical bone defects (8 mm).

In one study, cells genetically altered with BMP-2 were implanted and compared with cells treated with recombinant BMP-2 protein. The results revealed bone healing after 2 months; histologically the only difference observed was at the level of bone defects treated with bone marrow cells engineered to secrete BMP-2 because they induced the formation of a more robust bone trabeculae, whereas bone defects treated with recombinant BMP-2 had a thin and delicate appearing trabeculae.[16]

In conclusion, gene therapy is of great help for osteoinduction because it can be used to enhance the osteoinductive effect in mesenchymal cells to differentiate into osteoforming cells and the latter into osteoblasts, favoring the bone healing process.

Osteoconduction

Osteoconduction is a property of bone grafts and bone substitutes (biomaterials) that allow cell and tissue growth on, around and within their surface (Figure 8A).[9] In other words, the bone graft or biomaterial functions as an anchoring structure (scaffold) for osteoprogenitor mesenchymal cells to enter the bone defect where the graft is located, adhere to it, differentiate into preosteoblasts, and thus initiate the secretion of osteoid matrix. An osteoconductive surface allows bone growth on itself or within its pores and canals, leading to bone growth (Figure 8).[12]

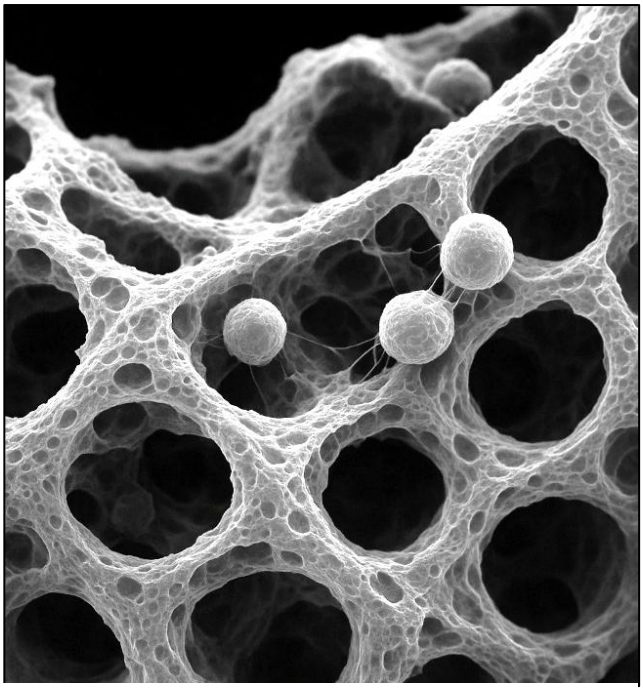

Figure 7. Bone substitute being surrounded by bone cells allowing osteogenic cells to form and growth osteoid matrix on and around its surface.

Osteoconduction is a process that takes place in three dimensions and is observed when a porous structure (the bone graft or substitute) is implanted within or adjacent to the patient's native bone. Thanks to the migration of capillaries, perivascular tissue, and osteoprogenitor cells within the porous structure of the graft, it is incorporated with the newly formed bone. This process is then characterized by an initial growth of fibrovascular tissue

that invades the porous structure, followed by the development of new bone directly over it. For this reason, the porous structure drives the growth of new bone within itself and along the fibrovascular tissue.[17]

Bone growth on the surface of the bone graft or bone substitute depends on the action of differentiated bone cells, which originate not only from activated preosteoblasts, but also from recruited mesenchymal cells through osteoinduction, thus osteoconduction depends on osteoinduction.

It is known that bone growth depends on an adequate blood supply, which explains why most of the growth factors such as insulin growth factor (IGF I and II), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) promote cell mitosis and angiogenesis in healing tissues.[12]

It is important to know that the porous surface of the graft or bone substitute is not a passive scaffolding structure; on the contrary, these materials are effective thanks to the chemical function of its surface, which has direct effects on the cells that arrive and make contact with it. The graft surface also serves as a site for a variety of bioactive molecules from the wound, including growth factors and adhesion molecules. This ability to bind or deliver bioactive molecules for wound healing makes many bone grafts potential vehicles for the delivery of exogenous bioactive growth factors.[18]

In conclusion, Osteoconduction is a process that occurs during bone repair and remodeling that requires a chemically active “porous surface”, presence of blood supply, an osteoinductive stimulus that attracts osteoprogenitor mesenchymal cells for the purpose of conducting and allowing bone growth on, around and into its surface.

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Osteopromotion

Osteopromotion refers to the capacity for “fusion” that occurs between the bone graft and the biological medium, and is due to the participation of some agents that, without being strictly speaking osteoinductive, facilitate biointegration; examples of these are products such as bone marrow aspirates, platelet concentrates and morphogenetic proteins (Figure 9).[10]

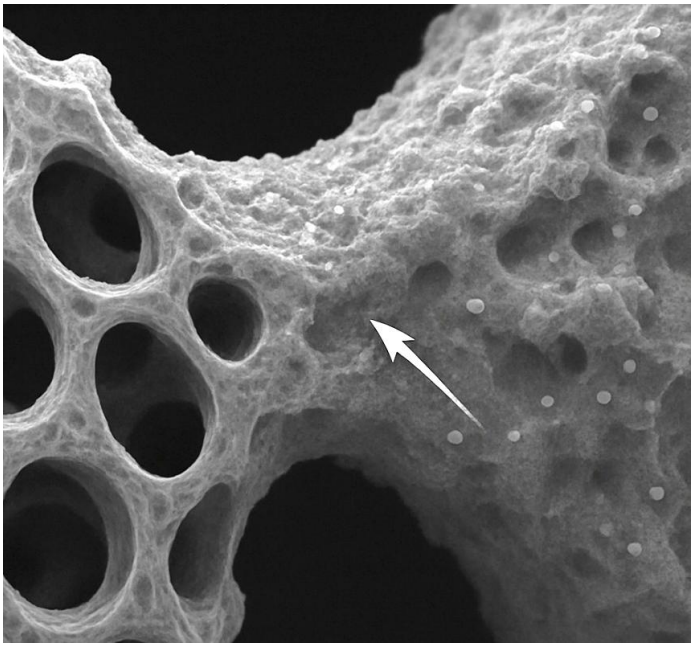

Figure 9. Photomicrograph reveals a decrease of the gap from 5.30mm to 3.60mm, after having performed the regeneration using a biomaterial, which exerted an osteopromotion effect by improving the biointegration of the graft and increasing its osteoinductive

Osteotransduction

The term Osteotransduction is described as the in vivo behavior of some biomaterials for bone regeneration that, after implantation in the bone defect, show a rapid biointegration and, simultaneously and gradually, a slow resorption allowing the replacement by bone tissue without leaving a space between the biomaterial and the patient's native bone, therefore, stability is not lost during this process.[20]

In vivo studies in rabbits, goats and sheep have shown that biomaterials such as phosphate cements are progressively transformed into bone tissue while maintaining the integrity of their structure; however, the speed of osteotransduction in rabbits was faster than in the other biomodels; therefore, osteotransduction is regulated by the bone remodeling process and depends on each type of species.[20]

In other words, osteotransduction refers to the ability of the biomaterial to increase osteogenic properties as well as to allow its replacement by the patient's native bone (Figure 10).[21]

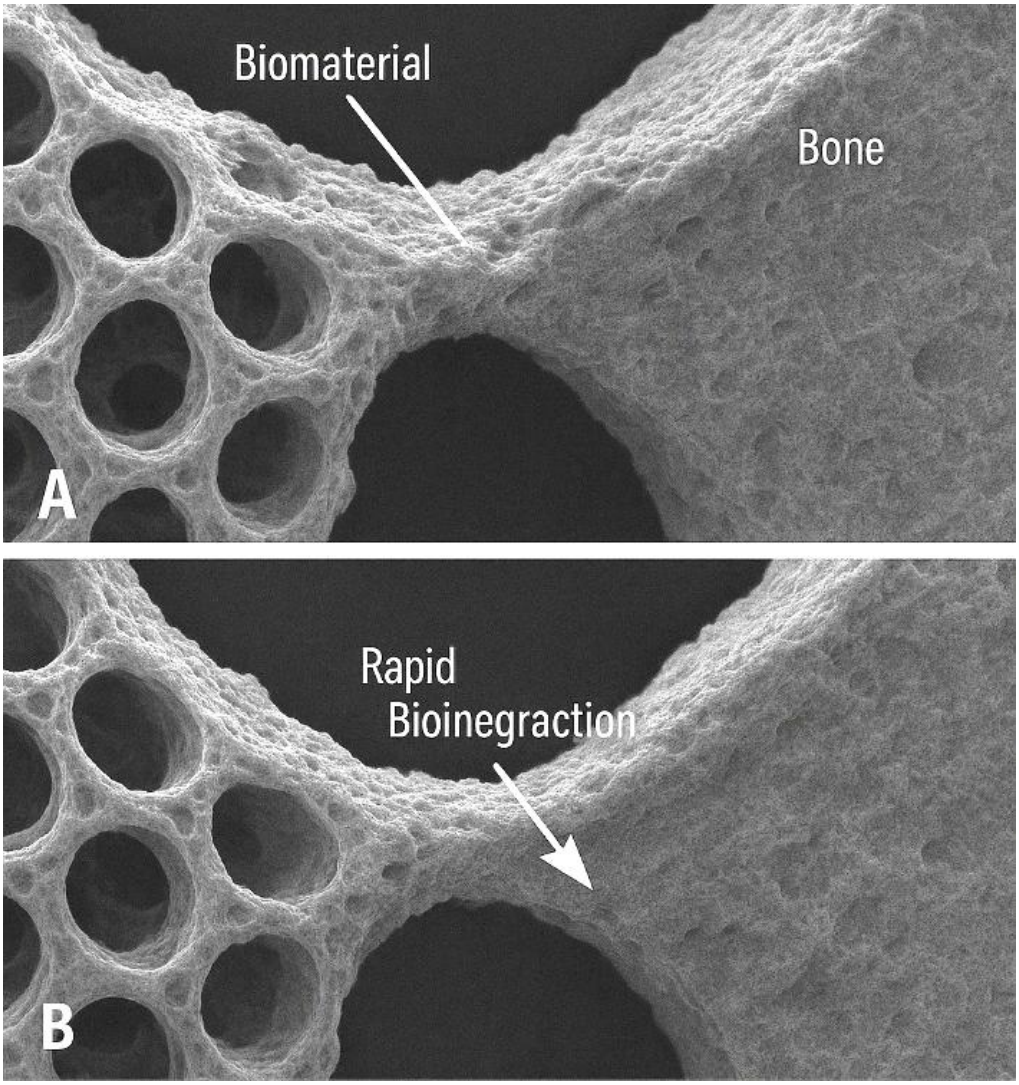

Figure 10. Photomicrograph showing the resorption of the bone graft and its replacement by the patient's bone tissue.

Origin of osteogenic cells

As their name indicates, osteogenic cells are capable of producing bone or differentiating into bone-forming cells. These cells are found in the periosteum, peri trabecular soft tissues and bone marrow, and are presumed to be derived from a group of undifferentiated pluripotent connective tissue stem cells, as well as vascular periocytes.[18]

Additionally, studies have revealed the presence of two osteogenic precursor cell populations: Determinate precursor cells (DOPCs) and induced precursor cells (IOPCs). The determined precursor cell (DOPC) is a stem cell that is predetermined to differentiate into an osteoblastic phenotype and proliferate without the need for an inducing stimulus when it has reached maturity. This cell type can be found on bone surfaces and in the stroma of the peri-trabecular medulla.[18]

In contrast, the induced precursor cell (IOPC) represents a pluripotent progenitor cell that is capable of differentiating into one or more varieties of connective tissue cells. IOPCs are much more immature cell populations than DOPCs but both cell populations are derived from the same pluripotent connective tissue stem cells (Figure 11). Given a specific stimulus, these cells can differentiate into bone, cartilage, fibrous tissue, muscle, adipose tissue and glial cells (Figure 12).

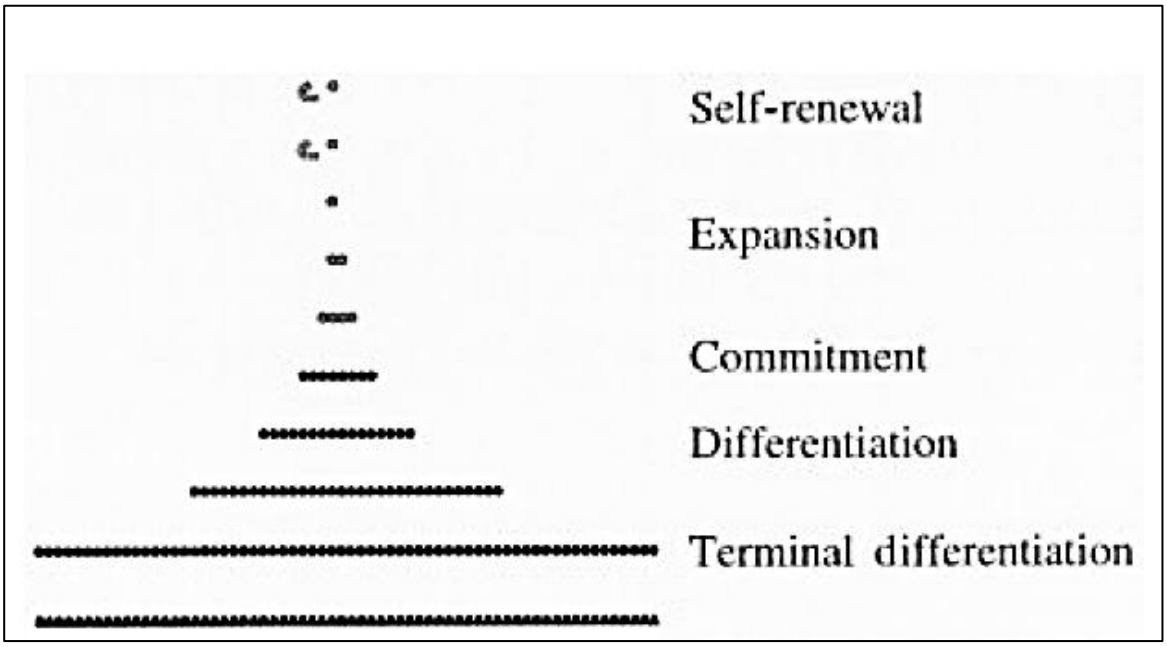

Figure 11. The expansion of proliferating progenitor cells is the result of the activation of resting stem cells. The number of progenitor cells expands exponentially. At one point during this expansion, the cells become committed to terminal differentiation, and just before they differentiate into osteoblasts, these cells can be considered induced osteoblastic progenitor cells (IOPCs). After commitment, cells destined to differentiate into osteoblasts can be considered as determined osteoblastic progenitor cells (DOPCs). Taken from Fleming et al, 2000.

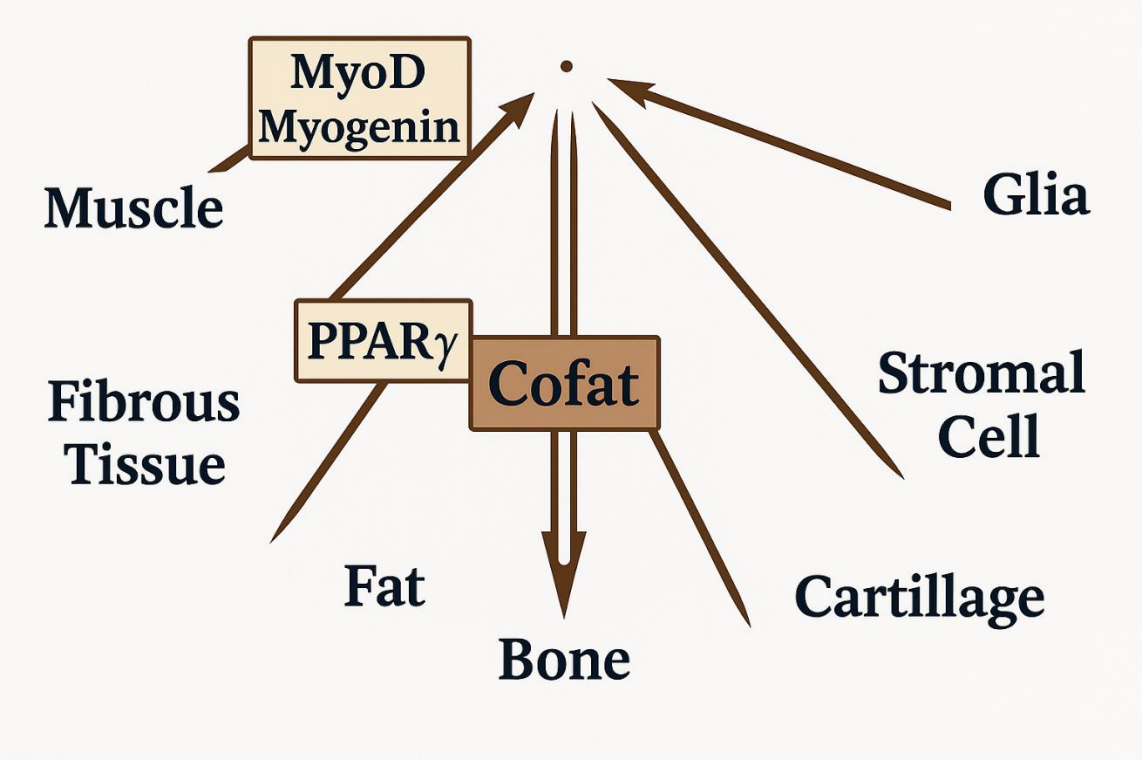

Figure 12. Possible lineage pathways for connective tissue pluripotent stem cells after differentiation events. Known genetic regulatory elements for pluripotent stem cell differentiation include: MyoD and Myogenin; PPAR-gamma (peroxisome proliferator-activated receptor gamma-activated receptor, and Cbfal (central binding factor transcription factor Alpha1). Taken from Fleming et al, 2000.

Bone marrow-derived pluripotent progenitor cells have been referred to by different names in the literature, such as marrow stromal cells, connective tissue progenitor cells, and mesenchymal stem cells. The name connective tissue progenitor cells is used mainly for two reasons: The first because stem cells can divide into two daughter cells; a proliferating daughter cell and a resting daughter cell, both of which are identical to the stem cell; and the second reason is because they are a histologically well-defined population of structural connective tissue cells of the bone matrix, which produce cytokines necessary for the maintenance of hematopoiesis (Fleming et al, 2000).[18]

Osteoblastic differentiation

The osteoblastic differentiation pathway is mediated and potentiated by various cytokines and osteotrophic factors (Figure 13). The differentiation of osteoblasts from a stem cell can be divided into the following phases. The initial proliferative phase, which is characterized by the expression of nuclear proteins (histone H4, c-fos and c-jun). After the expression of the transcription factor "central binding factor alpha-1 (Cbfa1), an upregulation of gene products for collagen type I, osteopontin, osteonectin and alkaline phosphatase can be found. The next phase is the matrix mineralization phase, which ends in a cell with an osteoblastic phenotype; this cell can be distinguished by its ability to express osteocalcin and bone protein peptide.[18]

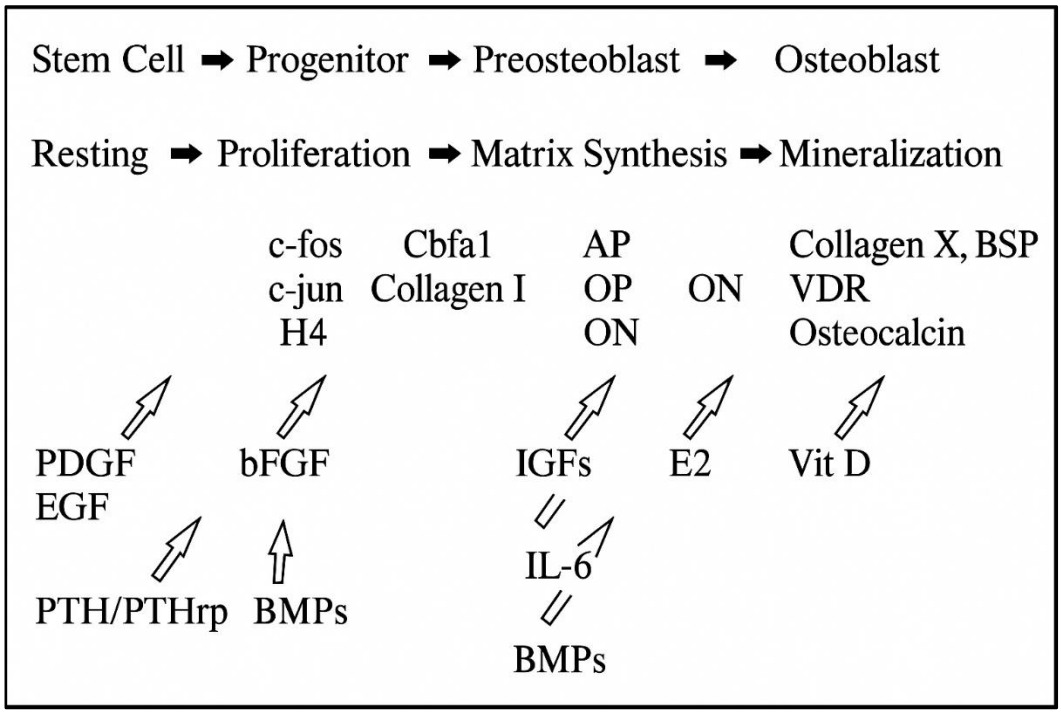

Figure 13. Osteoblast differentiation pathway. Description of the stages of osteoblast differentiation, the predominant differentiation activity of the cells at each stage, some of the characteristics of gene expression at each stage, the main site of action of most relevant osteotrophic hormones and growth factors. H4= Histone H4< Cbfa-1= central binding factor Alpha-1; AP= alkaline phosphatase; OP= osteopontin; ON= osteonectin; BSP= bone sialoprotein; VDR= receptor for vitamin D>; PDGF= platelet-derived growth factor; EGF= epithelial growth factor; bFGF= fibroblast growth factor; TGF-B= transforming growth factor-beta; IGFs= growth factor for insulin I and II; IL-6= interleukin-6; E2= estradiol; Vit D= vitamin D3;PTH= parathyroid hormone; PTHrp= parathyroid hormone-related peptide; BMP= bone morphogenetic protein family (Fleming et al, 2000).

In response to an inductive stimulus, stem cells may undergo one or more cycles of cell division. In one cycle, one proliferating daughter cell and one stem cell can be produced; in two cycles of cell division, one proliferating progenitor cell and two stem cells can be produced (Figure 11).[18]

After the production of daughter cells, a period of proliferation or expansion follows. During this phase, the number of progenitor cells expands dramatically. The number of mitoses between stem cell activation and their predetermined maturation is a critical variable in bone physiology because the number of times the daughter cells divide determines the number of mature osteoblasts and, therefore, the amount of bone formed after stem cell activation.[18]

The process of phenotypic maturation of cells involves a series of steps that begin during the proliferation phase. This process occurs in response to a combination of intra- and extracellular signals and, in turn, is mediated by changes in gene expression. Often this process is signaled by a small number of molecules called transcription factors. For example, the transcription factor Cbfa1 appears to be sufficient and necessary to induce a repertoire of genes associated with the osteoblastic phenotype; furthermore, it has been stated that Cbfa1 represents the linchpin for osteoblastic differentiation.[18]

The cellular predetermination phase is another critical variable in determining the amount of bone formed after stem cell activation. Because connective tissue cells are pluripotent, they can be induced to differentiate into different mature phenotypes (bone-forming cells, cartilage, muscle, fibrous tissue, adipose tissue and glial cells). For this reason, the pathway taken by one or more daughter cells for differentiation within the different phenotypic maturation pathways will determine the number of cells available to differentiate into osteoblasts.

CONCLUSION

Bone grafts or bone substitutes are biomaterials of different origins (autologous, animal, synthetic) whose properties can be used and potentiated for guided bone regeneration and guided tissue regeneration in the presence of bone defects caused by infection, trauma, or congenital defects as long as the clinician is aware of them. Knowing the biological process of bone formation is parampunt for clinicians who performe guide bone regeneration and guide tissular regeneration.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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