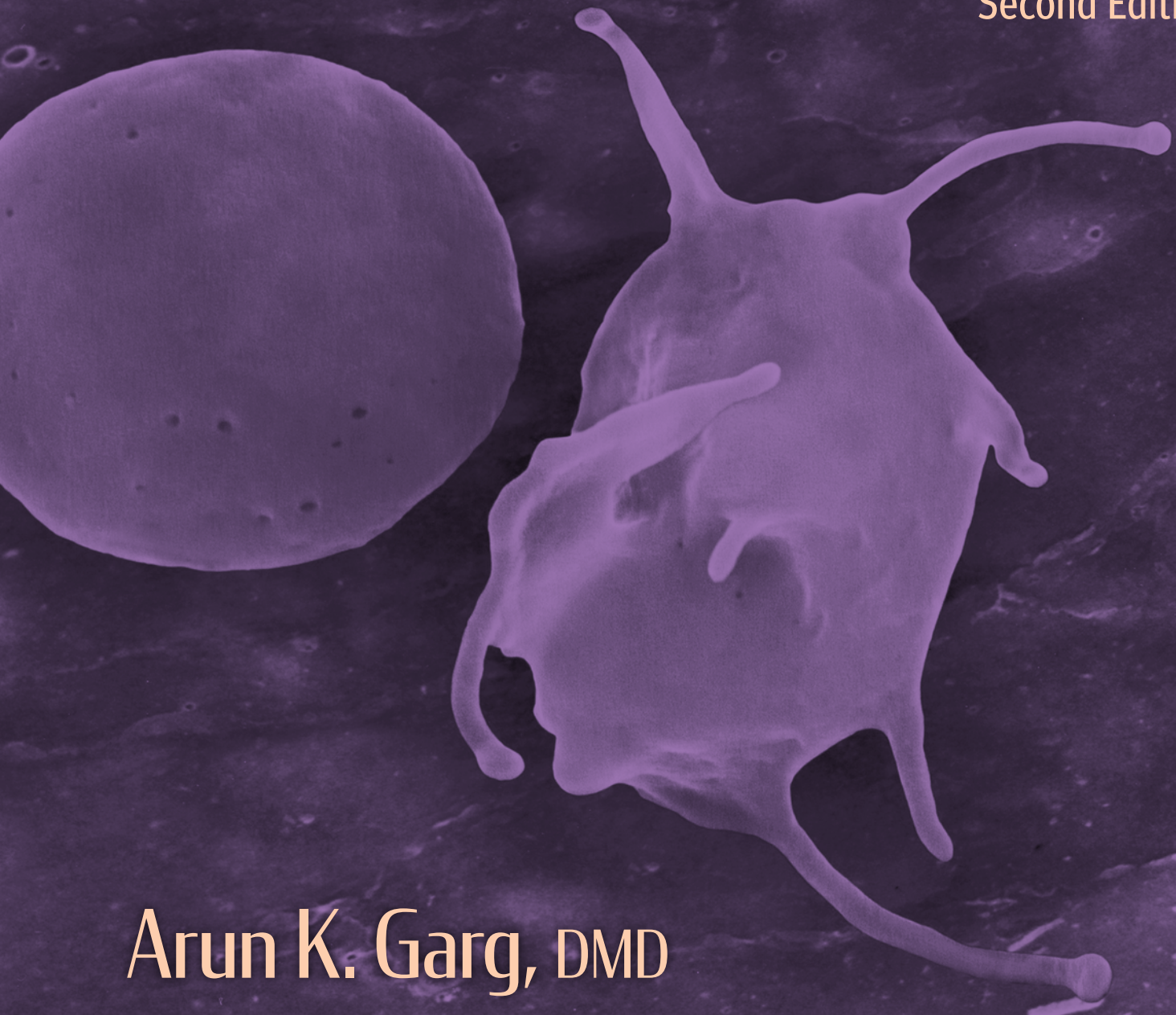
# Autologous Blood Concentrates

Second Edition



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# Autologous Blood Concentrates

Second Edition

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# Preface

In the nearly 25 years since Bob Marx and I developed the original formula for PRP, I have followed its gradual evolution from controversial idea to vital wound healing agent with keen interest—not unlike an anxious parent. In 2005, our co-authored book—*Dental and Craniofacial Applications of PRP* (Quintessence)—introduced the concept of platelet-rich plasma (PRP) to the world and provided scientific and clinical proof of its efficacy. Together, we spent the next decade training other clinicians on the proper use of PRP.

Everything changed in 2010, when it became public knowledge that PRP was the secret to Tiger Woods's speedy recovery from a torn ACL. Commercial interests quickly co-opted the conversation, drowning out the voices of those who, like Marx and me, did not want to see this low-cost biotechnology exploited by profit-hungry manufacturers of centrifuge devices. There was also an enormous amount of misinformation being promulgated by certain medical/dental experts who recognized the enormous therapeutic potential of autologous growth factors and seized the opportunity to establish a name for themselves in the scientific community. The medical literature became saturated with articles introducing new terminology to describe slightly modified growth factor compositions, often without much (if any) additional clinical benefit. The result was an alarming lack of standardization in protocols, a nomenclature best described as an alphabet soup of acronyms, and an overwhelming sense of confusion among clinicians. In 2015, when I published the first edition of this book, my primary motivation was to "set the record straight."

So the first edition of this book was my effort to refocus the conversation about platelet-derived therapies in order to make PRP accessible again to the practicing clinician. In titling the book, I made the major concession of using a generic term—autologous blood concentrates—as a way to signal my desire to focus on the science and not the politics. I wanted the book to reach clinicians regardless of which machine or nomenclature they were most familiar with.

In the world of regenerative biotechnology, 6 years is a very long time, and much has happened since the first edition of this book was published. This new second edition has been thoroughly revised, updated, and expanded to reflect current understanding, applications, and protocols of PRP for clinicians who have been using or wish to start using PRP in their practice. The centerpiece of this edition is a completely new chapter that details the step-by-step formulas and processes for preparing eight configurations of PRP and the specific indications for using each one. How and when to apply the various configurations in clinical dentistry—for soft tissue preservation, hard tissue preservation and regeneration, and facial rejuvenation procedures—is the subject of subsequent chapters. Because the use of PRP requires the clinician or an assistant to perform a venipuncture, the final chapter is a comprehensive guide to the principles and practice of phlebotomy.

I continue to engage in clinical PRP research, both in my private practices and through my charitable foundation, and will remain a passionate advocate for its use for the benefit of patients everywhere.

# Autologous Blood Concentrates: The Science of Natural Wound Healing

In many ways, traditional surgery and the medical arts have always tried to remove barriers to natural wound healing. Removal of these barriers proved that through replicable conditions and cases, standardized protocols could be created and followed to enhance wound healing. Over time, replication of results led to even more standardized techniques and procedures. For example, wound debridement and administering antibiotics demonstrably helped prevent infection, and stabilizing wounds and placing tissues in closer physical proximity promoted healing. These particular kinds of standardized, replicable surgical techniques can be labeled assistive or nonobstructive.[1] However, beginning in the last quarter of the 20th century, a truly "proactive" phase in surgical medicine began with the discovery that macrophages, reacting with oxygen, release growth factors that promote wound healing.[2–6] An assortment of cellular/tissue and oxygen-related therapies followed,[7–16] culminating only about two decades ago in the use of growth factors produced from concentrated autologous blood platelets to promote wound healing.[17–22] The result is medical science's present focus on platelet and other biologic/regenerative therapies as critical means for promoting, initiating, and sustaining wound healing.[23]

In the mid-1980s, platelets were understood essentially as cells that helped to stop bleeding. Over the next 20 years, the discovery of the various growth factors released by platelets gave birth to regenerative medical therapies, most of which are still in their infancy.[24–35] How the growth factors and functional matrix delivered by autologous blood concentrates induce wound healing is widely understood. The focus of current research is replicating and standardizing the preparation and administration of the autologous-derived product to best suit the donor-patient. Though a variety of preparation techniques, products, and nomenclatures have been tried, the good news is that no significant difference in the osteogenesis of growth factors has been evidenced.[36–40]

Nevertheless, firmly establishing the science of platelet-rich plasma and other platelet-derived products requires an investigation of platelet biology, the release of growth factors, and the practical application for soft tissue healing and bone tissue regeneration. So far, the scientific journey of autologous blood concentrates has been remarkably expansive. The future of this journey promises to be more focused, even single-minded, toward its scientific destination—even more standardized products and procedures based on replicable results.

## Platelet Biology

The first autologous blood concentrate was introduced in the literature as *autologous fibrin adhesive* and later changed to *platelet-rich plasma* (PRP). That term became standard, first in the oral surgery literature and then in all medical and dental surgical specialties. While many other terms have been used to describe autologous blood concentrates—particularly in niche markets as a way to sell specific centrifuges and/or test tubes—PRP will be used throughout this book.

As an actor in the performance of regenerative medicine,[41–47] PRP provides two of the three essential components for allowing a wound to heal in place: growth factors and a scaffolding stage (Fig 1-1). The third ingredient for

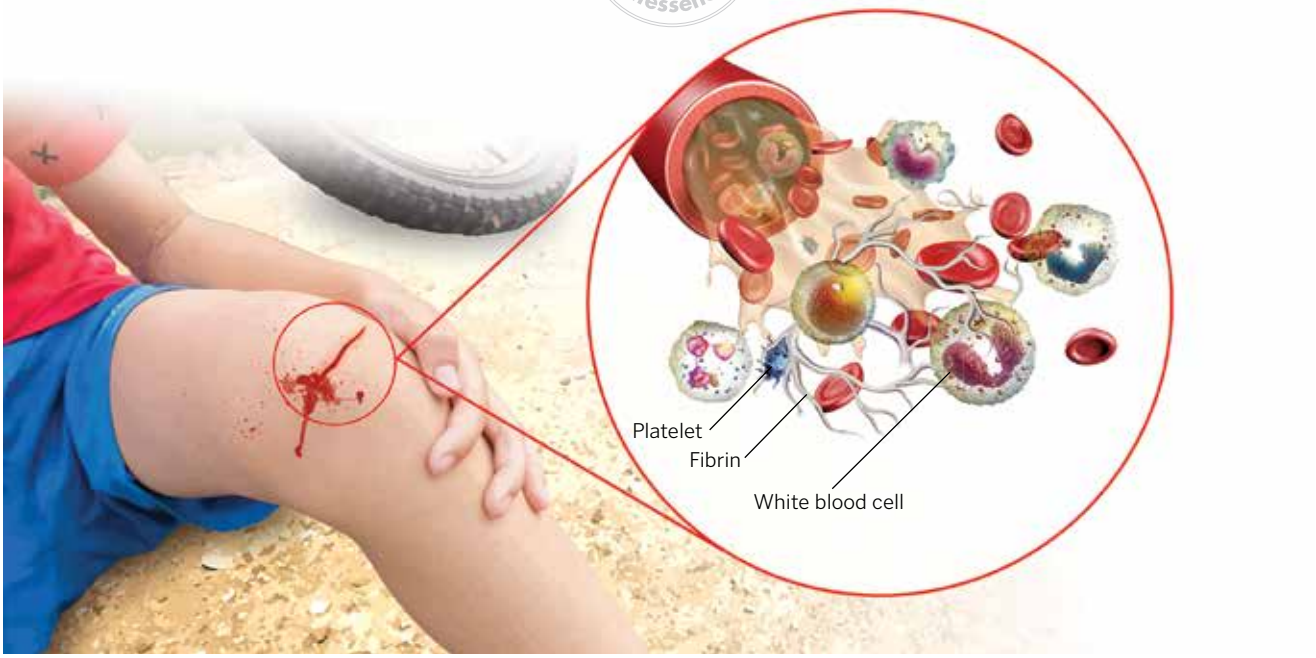


**FIG 1-1** Components of blood that are concentrated in PRP.

in situ tissue regeneration is the cells. PRP is a patient's own blood concentrate, modified in a relatively quick, efficient, safe, and simple procedure, to obtain a dense concentration of platelets. The autologous nature of PRP precludes disease transmission to the patient or other adverse reactions. To provide wound healing benefit to the patient, PRP generally must have at least four to seven times the normal concentration of platelets, or roughly 1 million platelets per microliter.[48] A blood clot in a wound consists mostly of red blood cells and much smaller percentages of platelets and white blood cells (Fig 1-2). Applying PRP to such a wound essentially replaces red blood cells with growth factor–producing platelets and a fibrin network, thus (at least in theory) greatly enhancing the healing of wounds and migration of cells, as well as the regeneration of bone and soft tissue.

When bone marrow megakaryocytes undergo cytoplasmic fragmentation, the anuclear platelet cells enter the circulatory system. The relatively tiny platelet is about one-fourth the size of a red blood cell (approximately 8 μm in diameter) and six to seven times smaller than a lymphocyte; however, the platelet's membrane extends pseudopodially via invaginations, which provide an expansive, dynamic, and vigorous surface area for the cell membrane during activation.[1,49] The plasticity and resilience of the platelet's pseudopodic membrane enable its vascular-sealing qualities, along with its ability to form a thrombus and fibrin clot, as well as clot retraction when its hemostatic labors are complete[50] (Fig 1-3). Generally, the larger and younger the platelet, the greater its hemostatic qualities and the greater the quantities of growth factors contained within it.[23,51,52]

The short lives of platelets (240 hours or less) are very actively spent synthesizing and secreting growth factors as part of the blood-clotting process. The platelet contains lysosomes, ribosomes, mitochondria, and an assortment of intercellular proteins that help form its shape as well as its mobility. The platelet cell also contains storage organelles that consist of lysosomal granules (for storing enzymes for digestion), dense granules (for storing and secreting adenosine diphosphate [ADP]), and alpha granules (for summoning and activating other platelets via nascent growth factors) (Fig 1-4).[53–55]

The growth factors stored in the alpha granules include platelet-derived growth factor (PDGF) isomers labeled AA, BB, and AB (referred to as polypeptide "dimers" because

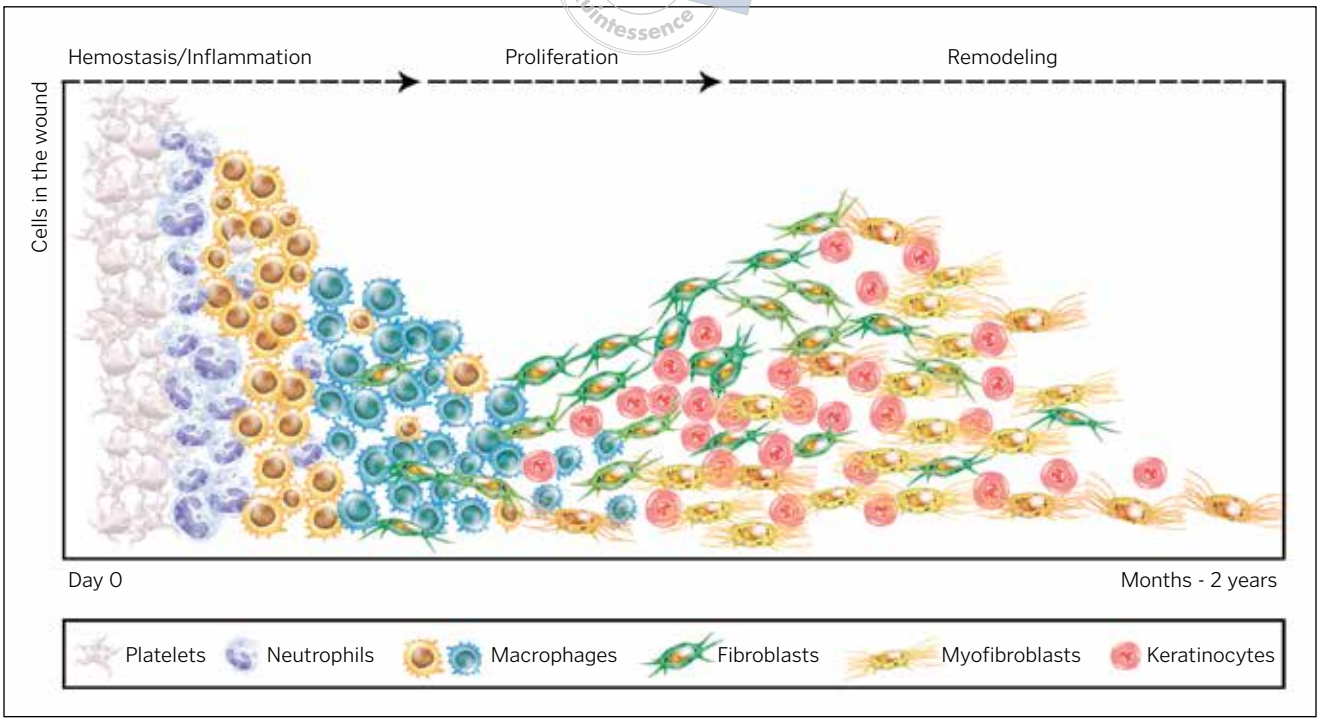


**FIG 1-2** The classic wound healing cascade.

of their two active sites, which are actually antiparallel monomers); transforming growth factor (TGF) isomers beta 1 and 2; vascular endothelial growth factor (VEGF); and epithelial growth factor (EGF). Growth factors not contained in platelets include insulinlike growth factors (IGF) 1 and 2 and bone morphogenetic protein (BMP). The blood-clotting process activates the alpha granules in platelets to secrete growth factors, both when the platelets circulate normally in the blood and when the platelets are concentrated in PRP. Alpha granules move toward the membrane and bind themselves to its surface, causing histone and carbohydrate side chains to combine with, and to activate, growth factor proteins.[1]

In addition to their basic hemostatic roles, platelets have been found to play a number of nonhemostatic functions.[56,57] Tissue repair and inflammation are two of several functions that researchers are currently exploring.[58,59] The alpha granules in platelets are the producers/directors of the diverse roles medical science is learning platelets can play beyond the traditional role of hemostasis. Ironically, in fact, the granules contain substances that normally work in opposition to each other. The platelet's ability (when properly signaled) to release different substances specifically

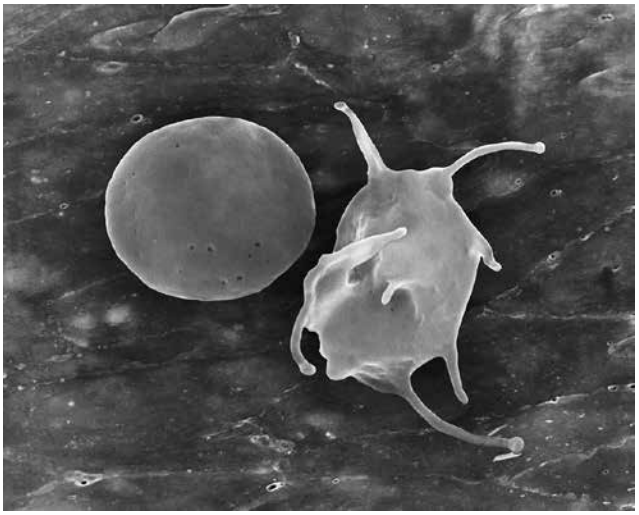

**FIG 1-3** Scanning electron micrograph (SEM) appearance of a platelet before *(left)* and after *(right)* activation.

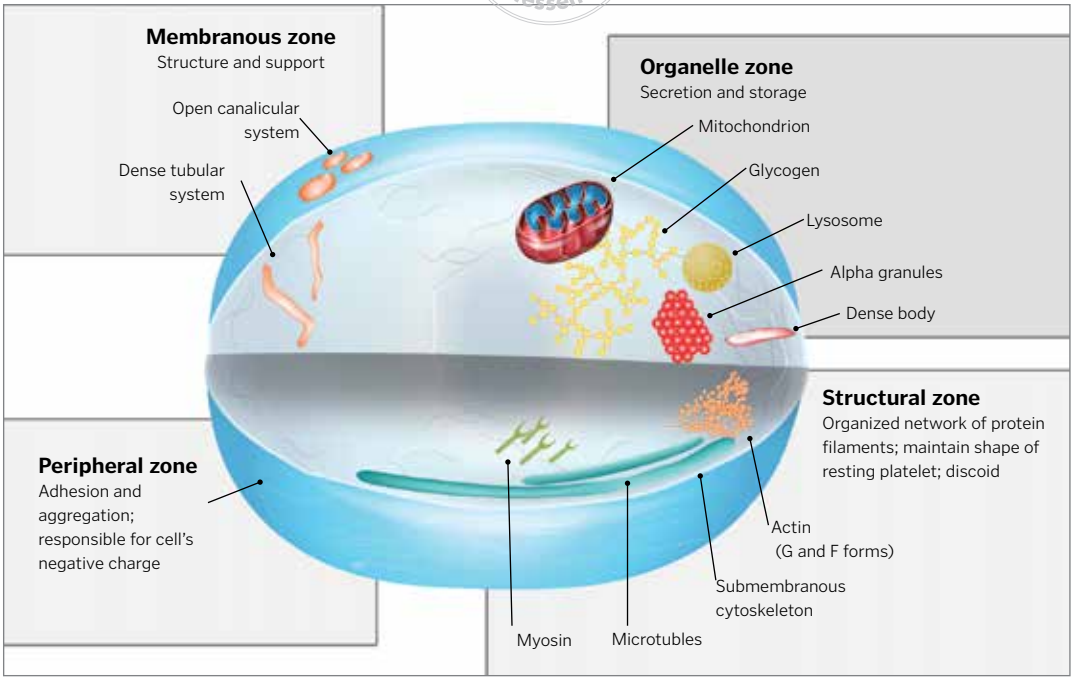


**FIG 1-4** Shape and functions of platelet cells.

required by other cells, molecules, and tissues explains why it is the focus of so many different types of current medical research, including tissue inflammation and regeneration, neurology, autoimmunity, hemostasis, wound healing, atherosclerosis, and a diverse range of others.[60-66]

## PRP Growth Factors

There are a number of different types of growth factors contained in platelets.[67-69] These growth factors are polypeptides, accounting not only for tissue and organ morphogenesis (from shortly after human conception to adulthood) but also for cell differentiation and proliferation. Their crucial activity in cell healing makes them especially important to current research in tissue engineering and regenerative medicine (Fig 1-5). The growth factors that have received the most attention from medical researchers and practitioners include PDGF-AA, PDGF-BB, and PDGF-AB; TGF-β1, TGF-β2, and TGF-β3; fibroblastic growth factor (FGF); IGF; EGF; and VEGF.

### PDGF

PDGFs, found in several types of human cells but mostly in platelets, were the first type of growth factor discovered in alpha granules.[27] PDGF adheres only to target cells with receptive surface membranes. When a wound is treated with concentrated platelets, the release of PDGF triggers activity in fibroblasts, neutrophils, and macrophages, stimulating the latter to additionally release growth factors that help to heal injured tissues.[70-72] Specifically, the target cells' transmembrane receptors are activated by the platelet-released growth factors, and the receptors' intracytoplasmic qualities activate the signal transducer proteins, one of which migrates to the target cell's nucleus. There, the protein initiates a particular, regulated gene sequence—which may, for example, include the production of osteoid.

Alternatively, the sequence might lead to the synthesis of collagen. The regulated nature of the sequence precludes an "overdose" of concentrated growth factors. Growth factors' amutagenic qualities testify to their ability as natural proteins to initiate and participate in the regular genetic activities associated with the controlled mechanisms for wound healing.[1,73-76] As isomers of a single protein, and functioning as mitogens, PDGFs—the most common growth factors—perform different but often complementary tasks (Fig 1-6). This prompts certain cells to replicate, specifically mesenchymal stem cells, osteoblasts (producing osteoid), endothelial cells (secreting basal lamina), and fibroblasts (producing collagen).[77-83]

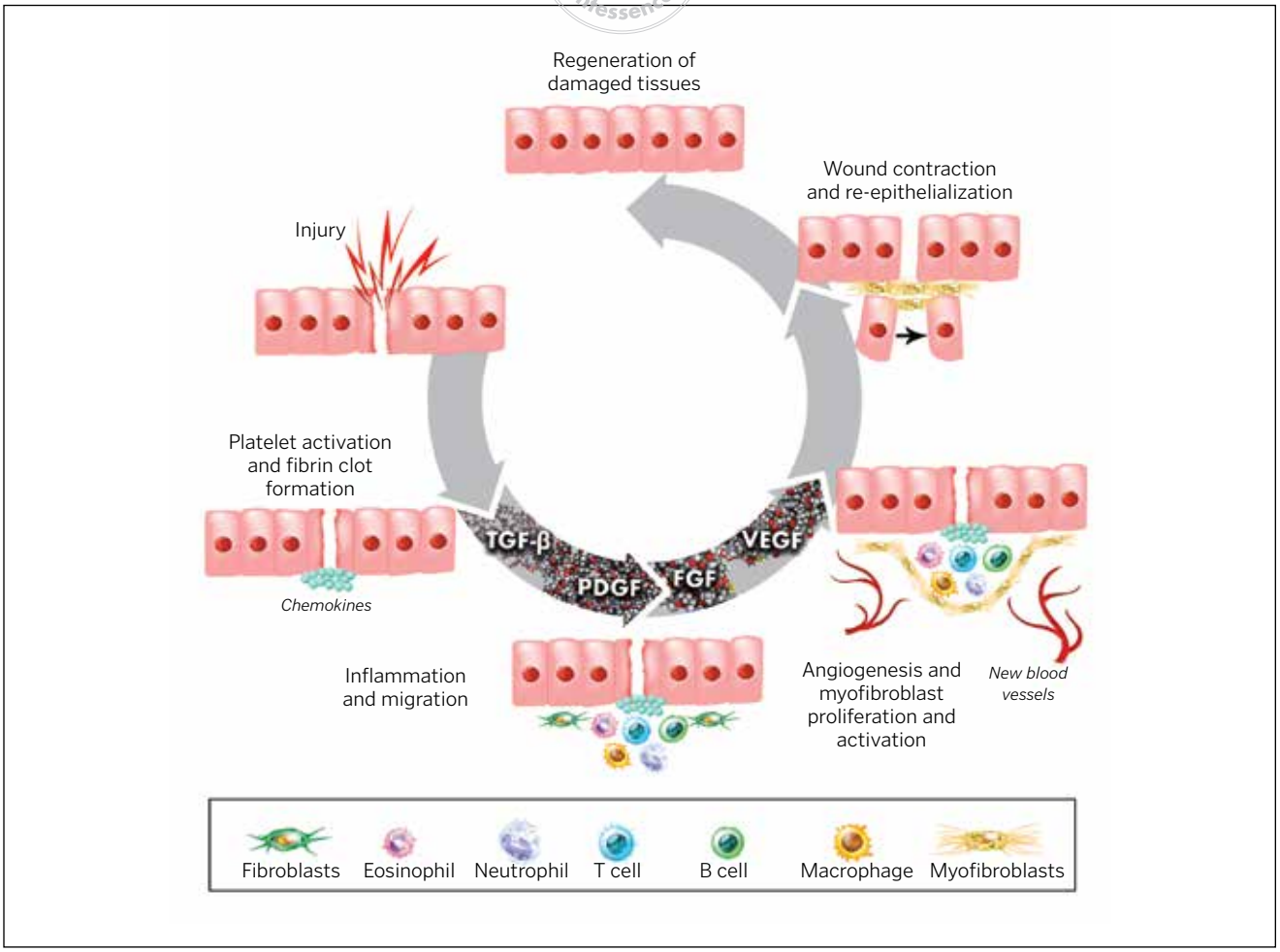


**FIG 1-5** Wound healing and tissue regeneration cycle.

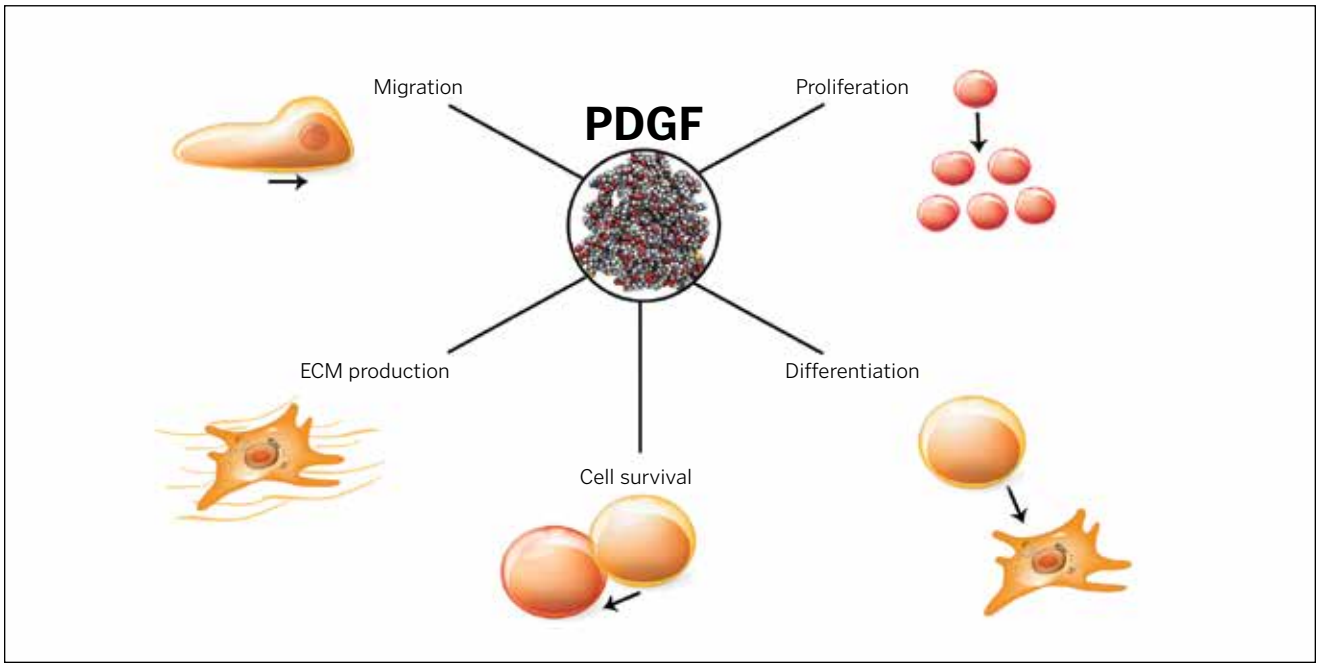


**FIG 1-6** Roles of PDGF.

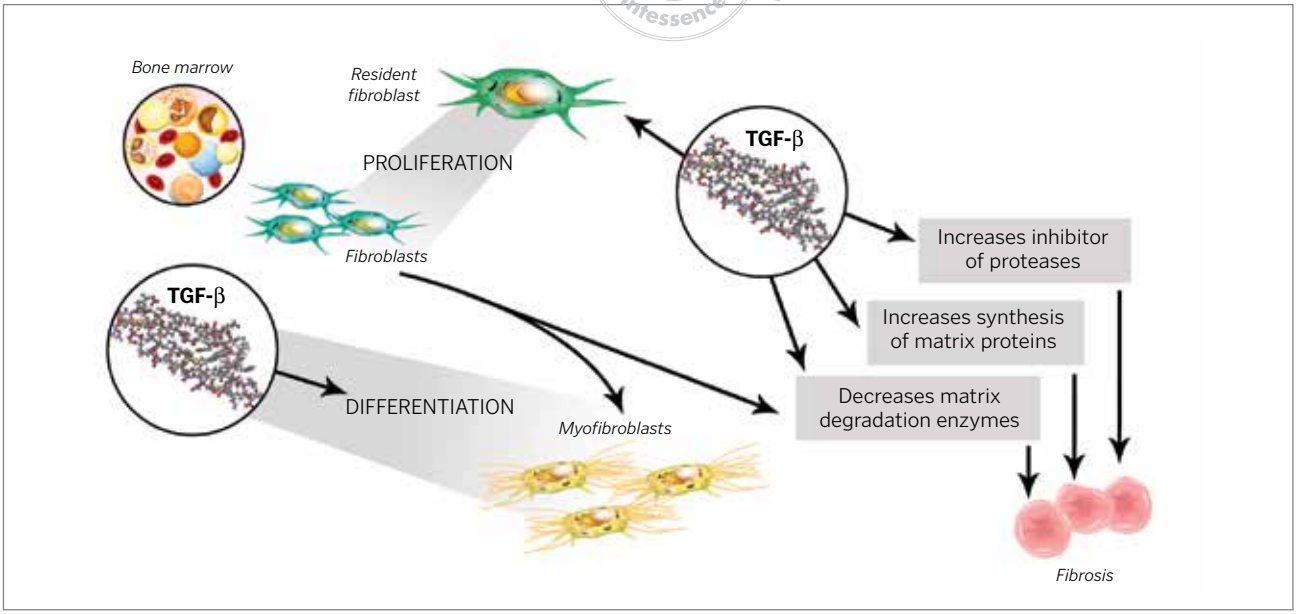


**FIG 1-7** TGF-β stimulates the proliferation and migration of fibroblasts and the process of epithelial-mesenchymal transition, but it also stimulates fibrotic responses, which can lead to end-stage organ failure in the heart, kidney, etc.

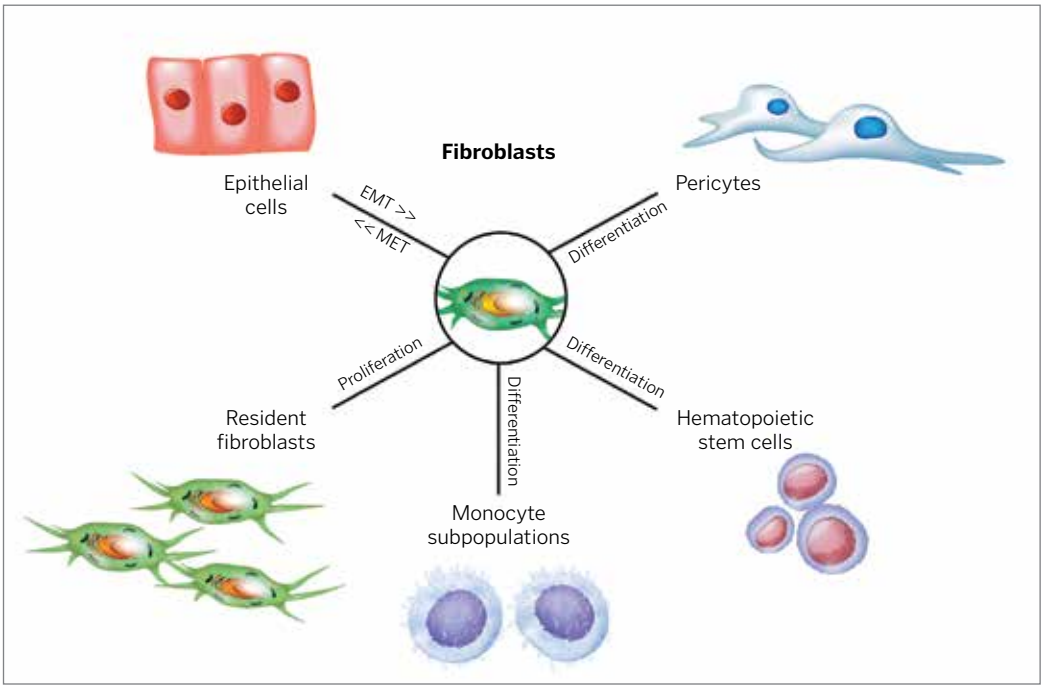


**FIG 1-8** Fibroblasts have different origins at different developmental stages (EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition).

## TGF-β1, TGF-β2, and TGF-β3

There are dozens of TGFs (including BMPs), and three of them (TGF-β1, TGF-β2, and TGF-β3) are protein growth factors that behave not only as mitogens (for cell replication) but also as morphogens (for cell differentiation).[84,85] As cell preservers, TGF-β factors serve essential functions in wound healing, from the fetus to the adult.[86–89] Like PDGFs, TGFs exert their influence in both healthy and pathologic cell activities, making their therapeutic use extremely problematic and challenging in that they often behave in opposite and even contradictory ways in both soft and hard tissues, including their roles in proliferation, migration, and differentiation[90–93] (Fig 1-7).

## FGF

FGF is an important mitogen inducer of fibroblast and endothelial cell proliferation. It also stimulates angiogenesis and plays a vital role in the repair of skeletal muscles and tendons. New blood vessel formation is due in large part to the activities of FGF, and it stimulates the migration of the macrophage as well as epithelium for epidermis formation[40,94,95] (Fig 1-8).

## IGF

IGFs are peptide hormones that have been found to promote cell growth in in vitro experiments. IGFs were also found to reduce levels of blood glucose in various tissues, hence their name. Their ability to stimulate glandular activities in humans differentiates them from other PRP growth factors. For example, IGF-1 mainly adheres to and stimulates receptors in cells of pituitary growth hormones. Most cells increase in size and number as a direct result of the synthesis and secretion of IGF-1 by tissues stimulated by growth hormones.

Growth factor production, along with growth hormone production and concentrations, wax and wane as part of the natural maturation process of humans before, during, and after pubescence, particularly for IGF-1. Liver production accounts for most IGF concentrations. IGFs have their most potent growth-stimulating effect on themselves and on nearby cells, and they (both IGF-1 and IGF-2) aid in bone cell mitosis. As an osteoblast secretion, IGF assists in osteogenesis and bone ossification via proliferation and differentiation of cells[96-98] (Fig 1-9).

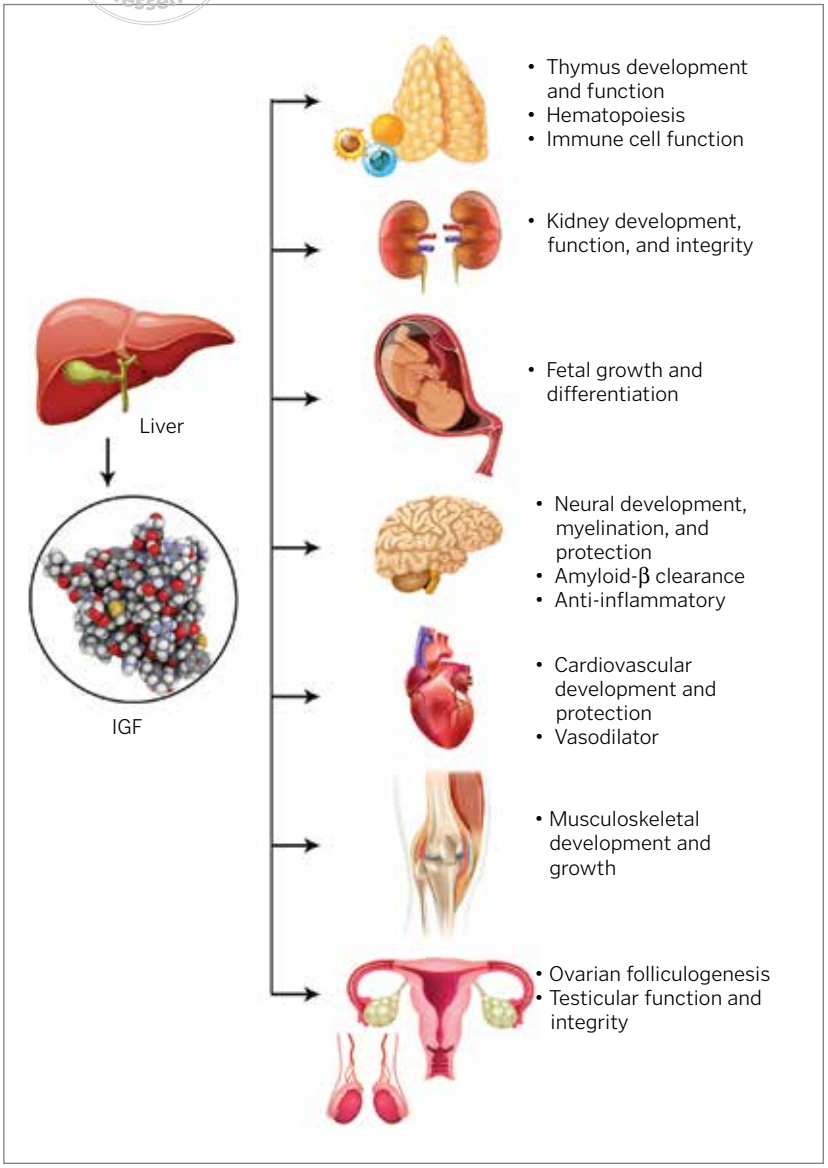


**FIG 1-9** Some of the roles of IGFs.

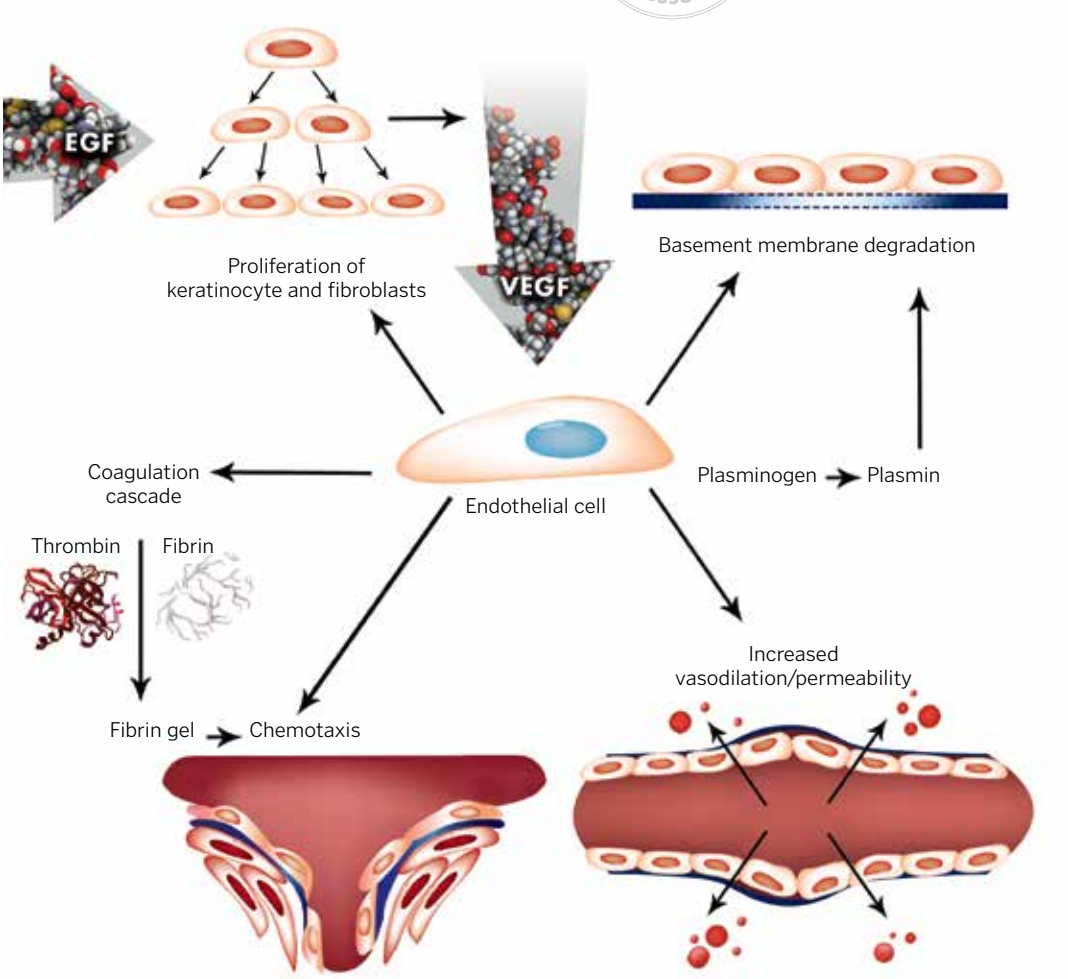


**FIG 1-10** VEGF stimulates the endothelial cell, enhancing multiple phases of the angiogenic cascade.

## EGF

The protein-based EGF causes the basal cells of the skin and mucous membranes to replicate, migrate, and form essential elements of these membranes.[99] EGF likely positively affects the generation of tissues as well as wound healing because of the way it controls the proliferation, growth, and migration of epithelial cells while strengthening the formation of new blood vessels. A therapeutic application of EGF has been used in preventing and treating dermatitis resulting from overexposure to x-rays or radium.

## VEGF

As its name suggests, the protein-based VEGF helps to develop blood vessels by interacting with endothelial cells, stimulating the synthesis of basal lamina, and recruiting pericytes[69,100] (Fig 1-10). Like several other growth factors, VEGF is known for and studied scientifically mainly due to its activity in pathologic states rather than healthy ones. The role it plays in the formation of new blood vessels of cancerous tumors has provided much of what we know of its abilities to stimulate growth in other cells. Tumors, just like healthy cells, can synthesize growth factor proteins—including VEGF—that promote the formation of new blood vessels from existing ones (angiogenesis). Instead of angiogenesis taking place for normal body growth or tissue repair, in this pathologic process it enables the spread of cancerous cells. In this case, VEGF activity leads to the development of capillaries within the tumor because of its stimulation of endothelial cells, which are the raw materials needed for angiogenesis. Endothelial cell division leads to the growth and migration of the tumor cells, developing a cascade of shared growth factors between their cells. Possible cancer therapies, therefore, include ways to introduce proteins into the tumor that slow or stop angiogenesis.

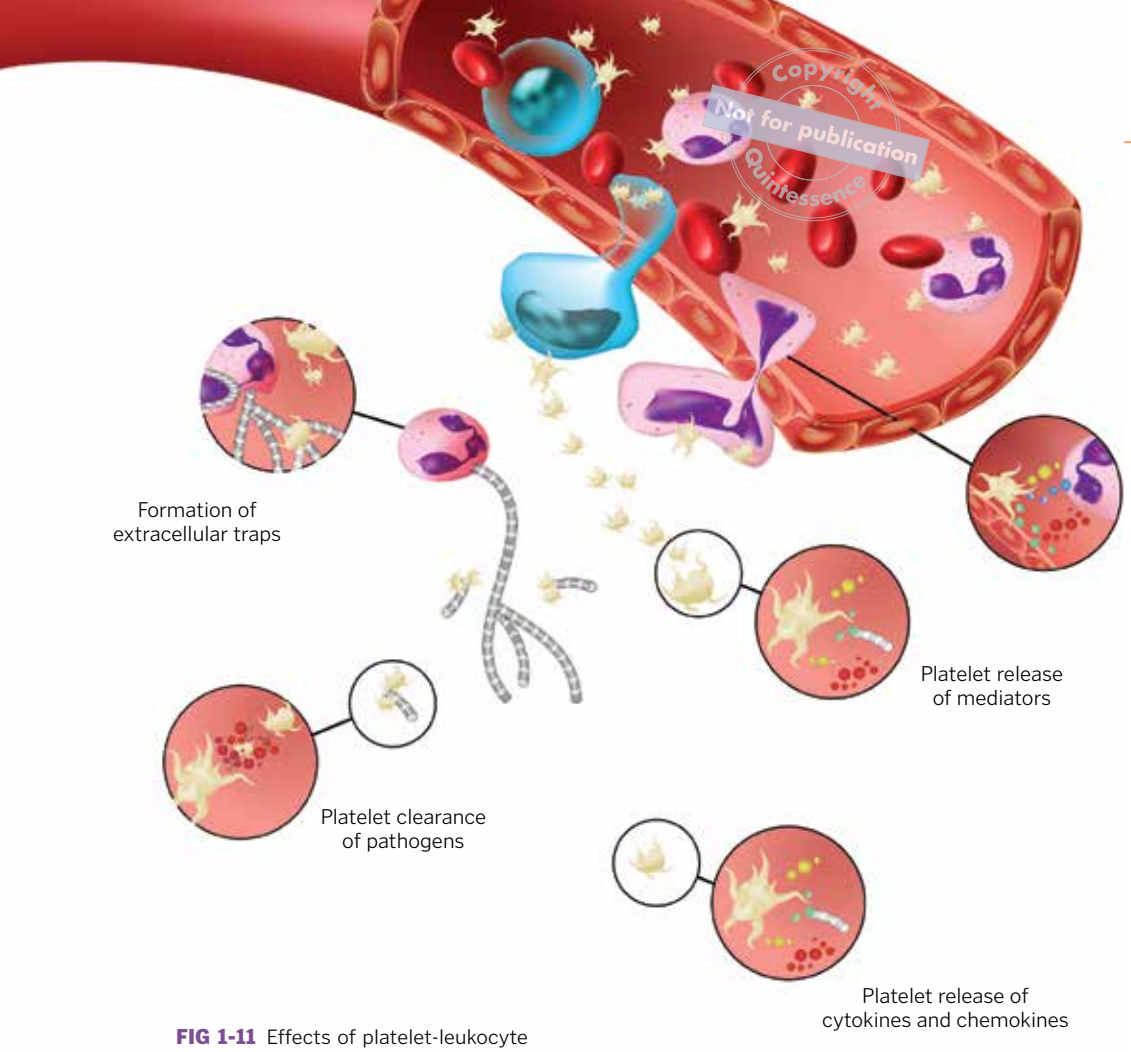


**FIG 1-11** Effects of platelet-leukocyte aggregates on differentiation, activation, and cytokine release.

## PRP and Soft Tissue Healing

PRP has shown great promise clinically and histologically, especially for healing soft tissue in a standard wound of a donor site for a split-thickness skin graft.[101,102] Additionally, healing therapies for burns may benefit significantly from PRP application. The platelets release growth factors and cell-signaling cytokines, such as interleukin and interferon, that act to regulate inflammation and infection in the immune system[103] (Fig 1-11).

When compared to non-PRP–assisted clotting, PRP-assisted clotting is remarkable for its rapidity of healing in the basal cells at the edge of the wound, where EGF induces epithelial proliferation; subsequent migration to the granulation tissue helps the clot's cell adhesion molecules. Unlike an unassisted clot, the PRP clot reveals the bundles of fibroblasts and collagen, evidence of an expanding epithelium, and more mature healing. This comparatively accelerated maturity is also evidenced by increasingly reduced vascularity and fibroblastic cellularity over time, as well as quicker fleshlike appearance in 2 to 6 months. Reduced pain in the first 7 days of the wound, and reduced scarring over time, are also notable differences effected by the PRP clot. These benefits are also demonstrated in healing of other soft tissue wounds, including mucosal flaps, dermal fat grafts, and similar wounds.[1]

Bone and soft tissue healing can be strengthened in a variety of surgical procedures when a concentrated mixture of autologous platelets is placed at the wound site. The relative ease of methods for obtaining PRP makes it an attractive regenerative adjunct therapy for many surgical treatments. Promoters of PRP tout its ability not only to help restore damaged bone and soft tissue but also to enhance wound healing, lower the patient's pain and discomfort after the surgical procedure, and reduce the rates of infection and loss of blood.[104–106] Much of the recent

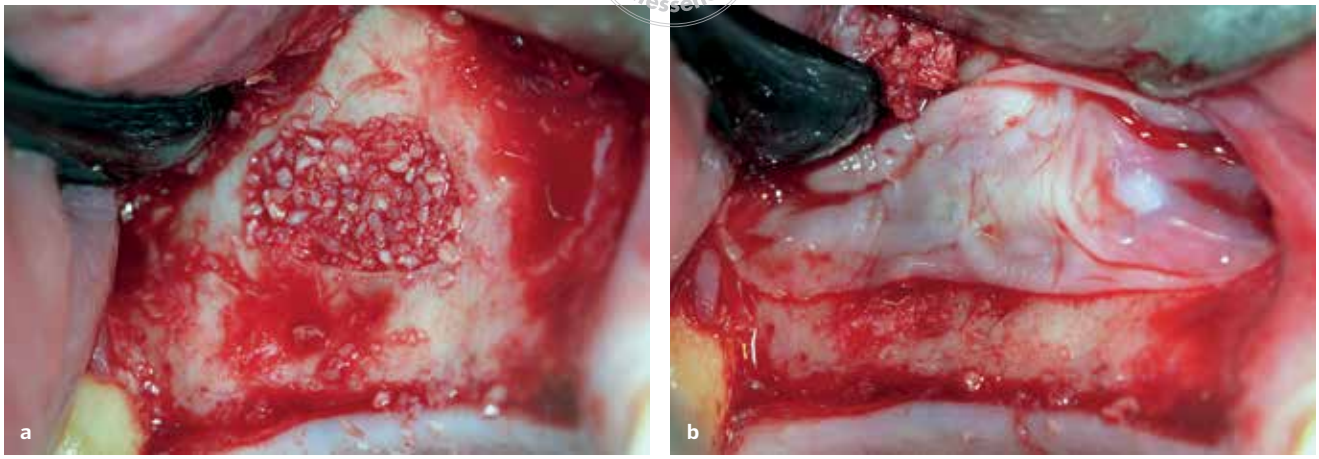


**FIG 1-12** Application of PRP in a sinus elevation procedure. *(a)* Once an adequate volume of graft material hydrated with PRP liquid has been placed, the window is ready for a PRP membrane. *(b)* The PRP membrane is placed over the lateral window, and then the flap is sutured back in place.

literature on PRP has been devoted to its wide range of applications in tissue healing and repair, including maxillofacial, periodontal, oral (Fig 1-12), and plastic surgery; heart and spine surgery; and chronic ulcers of the skin and soft tissue.[107–110] Some studies have suggested that in addition to enhancing wound healing, PRP provides antimicrobial qualities to inhibit postoperative infections in oral surgery.[111] PRP has been used in such soft tissue therapies as ligament, muscle, and tendon repair[38,112]; rotator cuff tears[113–115]; skin ulcers[116,117]; acne scarring[118]; and limb amputation.[119–121]

## PRP and Bone Regeneration

PRP accelerates and expands cells' wound healing response and acts biochemically to set the rate and amount of regeneration in bone. Within 10 days, its activity is complete, but this short action has long-lasting effects. For example, the alpha granules in platelets degranulate within several minutes of clot formation, and within 1 hour 90% of their growth factors are released, stimulating osteoprogenitor, endothelial, and mesenchymal stem cells. A graft-surrounding matrix is formed by fibrin, fibronectin, and vitronectin. PDGFs have a mitogenic effect on osteoblast, endothelial, and mesenchymal stem cells. The latter are also acted upon mitogenetically and angiogenetically by TGF-β isomers, which induce osteoblastic differentiation as well. While capillary ingrowth is promoted by VEGF, the lack of epithelial cells renders EGF inert (Fig 1-13a). Within about 72 hours, osteoprogenitor cell mitosis begins and capillary buds appear (Fig 1-13b). In the entire first phase of bone graft healing (about 2½ to 3 weeks), the graft is penetrated by capillaries, and osteoprogenitor cells have greatly proliferated (Fig 1-13c). During this phase, cell instability and infection are common, with the potential for lysing and arresting the development of wound healing. Obviously, prevention of infection and contamination are essential, as is graft stability.[1]

The hypoxic and acidic atmosphere of the wound itself attracts the circulating macrophage and blood monocyte (soon a wound macrophage), both of which assist bone regeneration via the secretion of more growth factors. The clot now contains fibrin, fibronectin, and vitronectin, acting as a matrix for the ingrowth of blood vessels as well as the proliferation and migration of cells. Between 3 and 6 weeks, the proliferation and differentiation of osteoprogenitor cells in the matrix produce osteoid (Fig 1-14), which signals the next (second) phase of healing, when graft and bone join and when adventitial cells develop to support the vascular ingrowth (Fig 1-15). Hypoxia diminishes due to the oxygen provided by the increased blood flow, preventing hyperplasia. By week 6, osteoclasts resorb the osteoid, releasing BMPs and IGF factors 1 and 2, causing the differentiation of nearby osteoblasts and mesenchymal stem cells for maturing bone replacement (Fig 1-16). Mineralized dense bone thus becomes the normal formation now, in the third phase

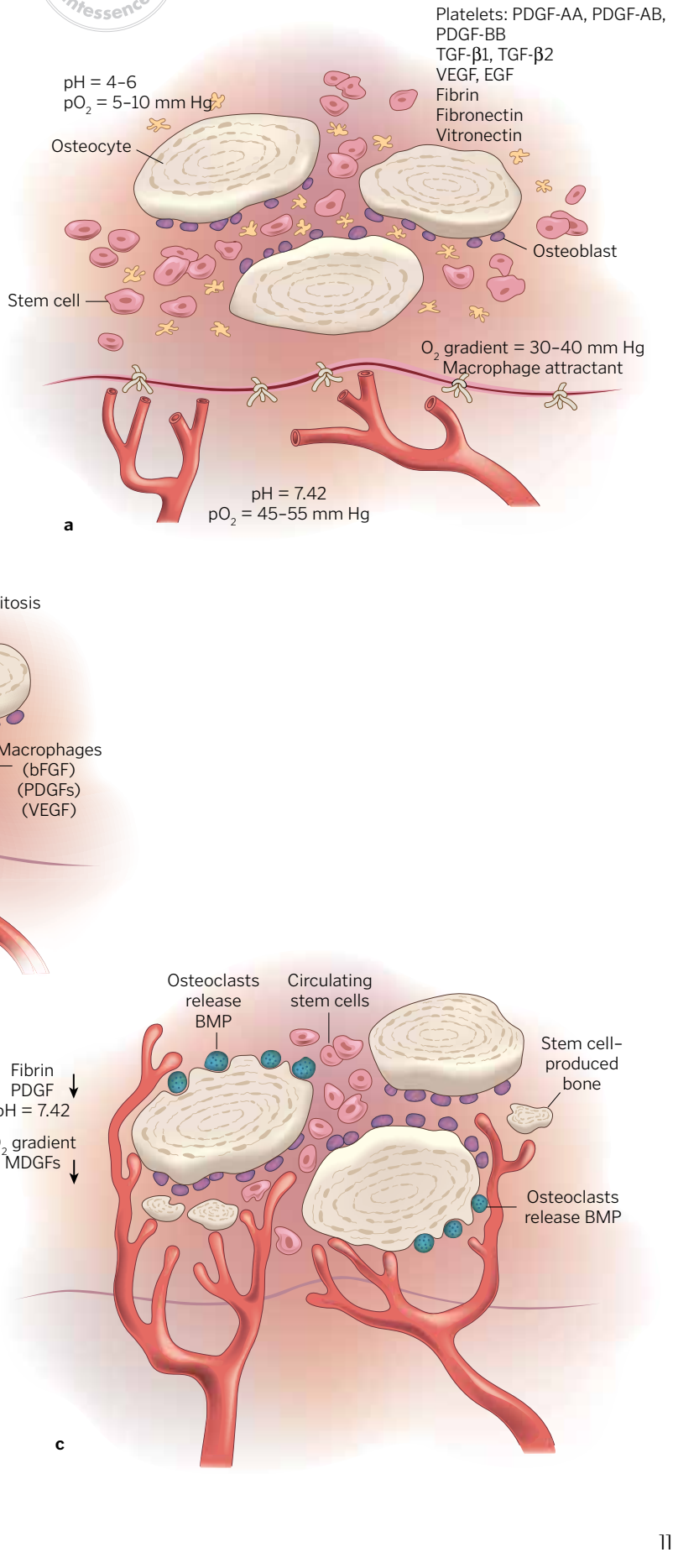


**FIG 1-13** *(a)* The biochemical environment of an autogenous bone graft. *(b)* As early as 3 days after graft placement, significant cell divisions and penetration of capillary buds into the graft can be seen. *(c)* By 17 to 20 days, complete capillary penetration and profusion of the graft has taken place, and osteoid production has been initiated. (Reprinted with permission from Marx and Garg.[1])

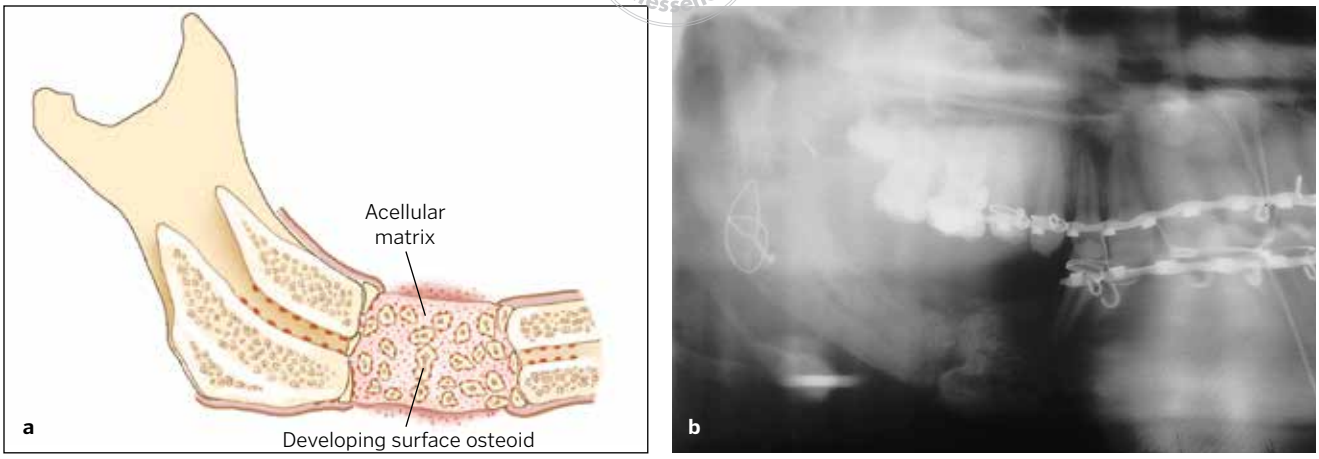


**FIG 1-14** *(a)* Acellular matrix along with surface osteoid developing on the endosteal surfaces of the transplanted bone and the resection edges of the host bone in a 3-week autogenous bone graft. *(b)* Corresponding radiograph shows a not-yet-mineralized graft with a "cloudy" appearance indicative of a graft that is not yet consolidated. The radiolucent line between the graft and host bone is the result of a dying-back resorption of the host bone from periosteal reflection. (Reprinted with permission from Marx and Garg.[1])

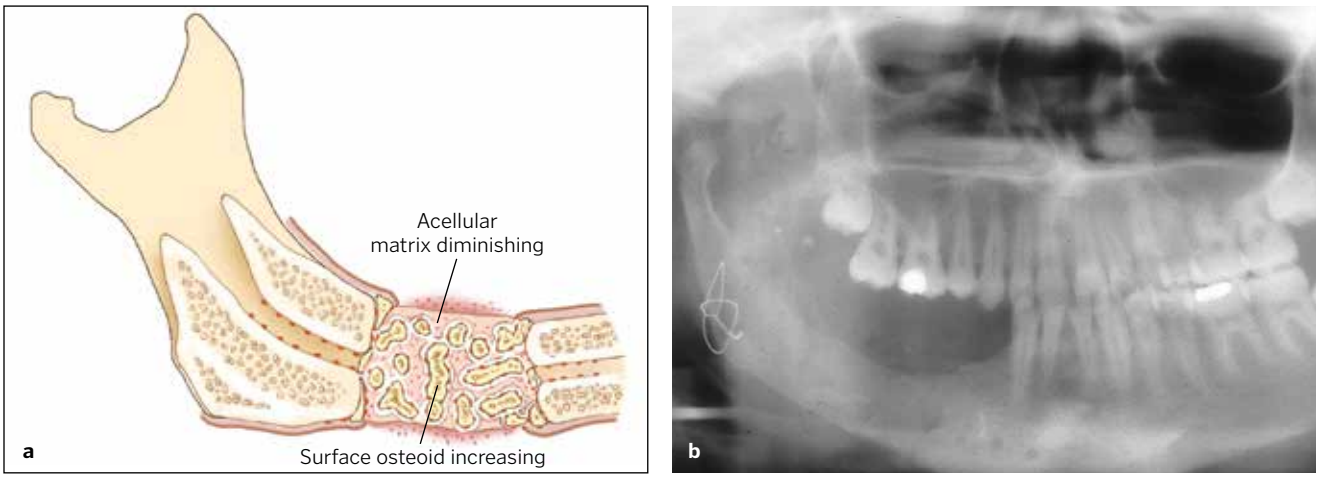


**FIG 1-15** *(a)* By fusing graft particles together and to the host bone, the graft has produced sufficient osteoid to consolidate by 6 weeks. *(b)* Corresponding radiograph shows condensation of the cloudy graft appearance, indicative of osteoid production and graft organization. The radiolucent line between the graft and host bone has nearly disappeared as a result of osteoconduction between the graft and host bone edge. (Reprinted with permission from Marx and Garg.[1])

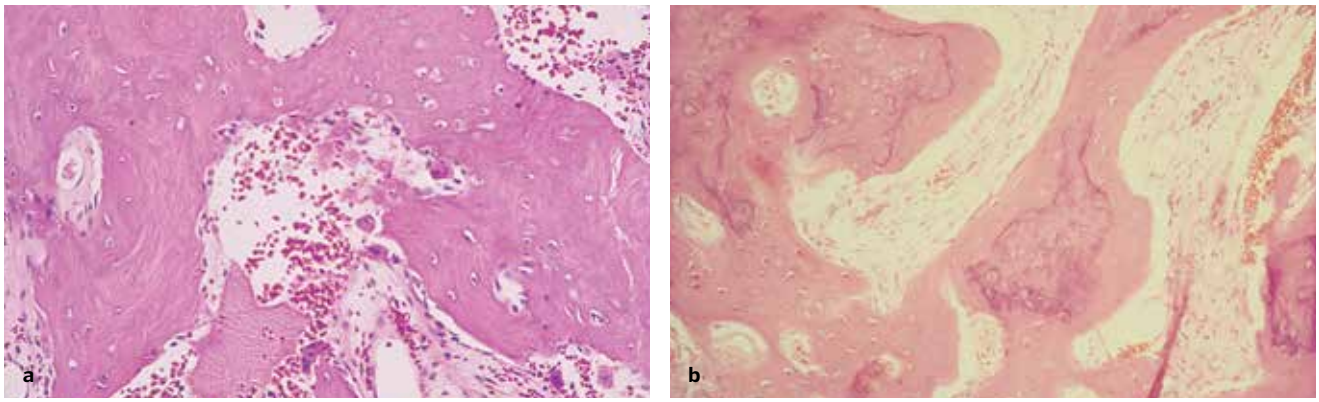


**FIG 1-16** *(a and b)* At about 6 weeks, the graft begins a major resorption-remodeling cycle in which osteoclasts resorb the disorganized immature bone and release BMP and insulinlike growth factors, thus inducing formation of new bone that will mature during function. (Reprinted with permission from Marx and Garg.[1])

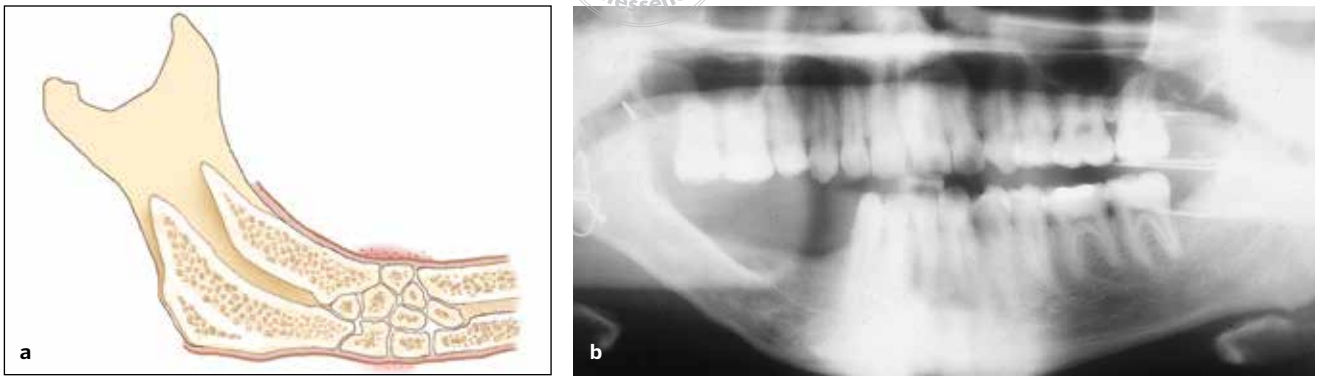


**FIG 1-17** *(a)* After 6 weeks, the graft will be consolidated and fused to the host bone. It then enters the lifelong resorption-remodeling cycle of the remainder of the skeleton. *(b)* Radiographically, bone maturation is characterized by the development of a normal trabecular pattern and an increased density. Here, an inferior border outline, an external oblique ridge, and a coronoid process attest to the remodeling of bone under function. (Reprinted with permission from Marx and Garg.[1])

of bone regeneration, as the graft-fused bone life cycle parallels the regular turnover rate of bone replacement in the body (Fig 1-17).

Platelet growth factors not only induce bone cell regeneration but also double the normal increase in mineral density in bone, with faster-forming and more quickly maturing bone, including significantly increased trabecular bone values[48] (Fig 1-18). Bone-related therapies for PRP include oral and cranial surgery,[48,122–124] spinal fusion,[125–128] osteogenesis distraction,[129–131] foot and ankle fractures,[132–134] bone grafting,[135,136] oral implants,[137–143] and diabetic fractures.[78,144,145]

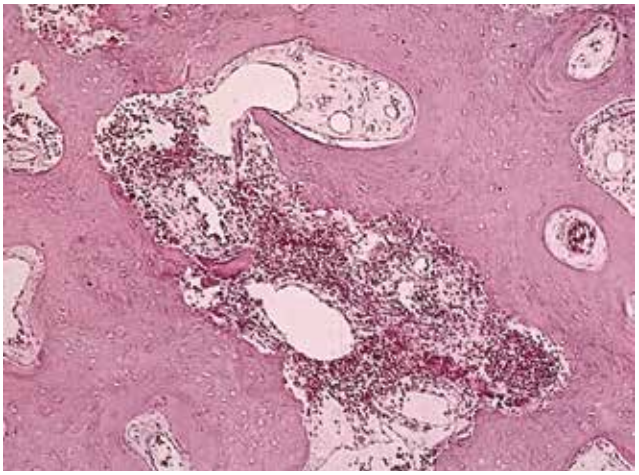

**FIG 1-18** Histomorphometry of an autogenous bone graft without PRP at 4 months shows that the graft has a 60% trabecular bone density, consists mostly of immature bone, and is undergoing active resorption-remodeling. (Reprinted with permission from Marx and Garg.[1])

## What Is PRP?

Efforts to standardize protocols for the clinical application of autologous platelet-derived product have often been accompanied by nonstandardized nomenclature for that product. Many researchers believe the term *platelet-rich plasma* is too general and incomplete, leading to confusion not only in preparation and application but also in cataloging in the scientific databases, thus hampering the flow of information in the scientific community. Other names that have been applied over the years include *platelet-rich fibrin* (PRF), *autologous platelet-rich plasma* (aPRP), *platelet gel* (PG), *autologous platelet concentrates* (APCs), *preparation rich in growth factors* (PRGF), *platelet-derived growth factor* (PDGF), *platelet-leukocyte gel* (PLG), *concentrated growth factors* (CGFs), and numerous others (Fig 1-19).

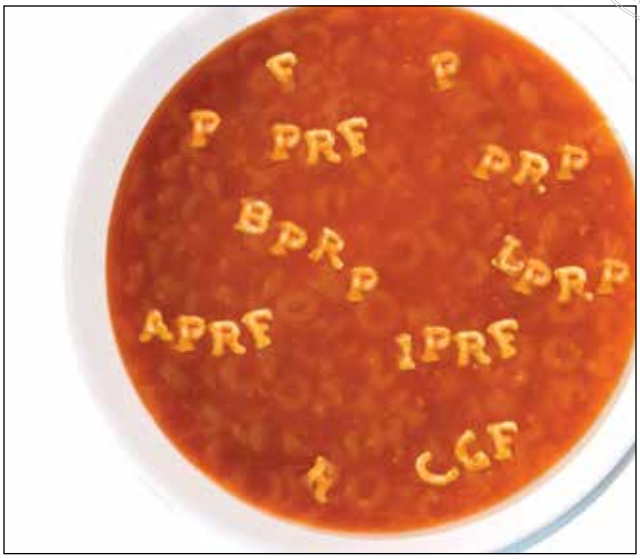


**FIG 1-19** The terminology for PRP is a confusing alphabet soup of acronyms. Chapter 4 presents the names and formulations for eight configurations of PRP and the step-by-step instructions for preparing them.

A simplified terminology-classification system for platelet concentrates has been widely adopted. It consists of eight categories based on its consistency and clinical application. The researchers and clinicians who devised this classification system believe it underscores the profound potential of these products and the need for all stakeholders to learn and demonstrate their awareness of the products' complexity. The composition and application of these other forms of PRP are detailed in the chapters of this book.

Historically, the majority of studies of the clinical efficacy of PRP did not provide sufficient information to allow their PRP preparation protocol to be reproduced. This not only added to the confusion over terminology but also made it impossible to compare the PRP products that were being tested. Several recent papers have addressed this confusion and shared ideas about how to standardize the protocol to make PRP preparation simple and straightforward, and most importantly, to obtain a consistent and effective platelet yield.[146–148] In 2017, Chahla et al published a systematic review of the clinical orthopedic literature on PRP and a call for more standardized reporting of PRP preparation protocols and composition.[146] Although 105 studies met the inclusion criteria for analysis, only 11 of them (10%) provided sufficient detail of their preparation protocol to allow it to be reproduced. Additionally, only 17 studies (16%) provided quantitative metrics on the composition of the PRP product they delivered to patients.

## Ongoing Controversies

Since the mid-1990s, clinicians have used an assortment of PRP preparations in several different therapies, ranging from oral and maxillofacial surgery and implantology to orthopedic surgery, burn treatment and the treatment of other wounds difficult to heal, soft tissue cosmetic surgery, soft tissue disease and injuries, and tissue engineering. Invariably, the literature that documents these therapies calls not only for high-level studies to better measure the efficacy of the variety of PRP therapies but also for standardizing the preparation and application of platelet-derived products.[1–4]

Any discussion of PRP application must be preceded by a review of platelet sequestration principles. Only then can a discussion of progress toward consensus on PRP protocols take place. Such an approach reveals that the clinical preparation and application of PRP across medical disciplines is a dynamic, evolving process, and that we disrupt this dynamism at our medical/scientific peril. Too-hasty attempts to reach consensus could inhibit researchers' efforts to discover the full potential of PRP and other biologic therapies.

### Naming and classifying platelet derivatives

Nearly 25 years after the earliest reports appeared, the literature on PRP for both human and veterinary medicine still lacks consensus on standardized protocols for preparing, naming,

Table 1-1 Factors that influence the quality of platelet concentrates

| Preparation step | Critical factor | Details |
|---|---|---|
| Blood collection | Needle | Gauge, length, material, surface modification |
| | Tubing of butterfly needle | Diameter, length, material |
| | Syringe/tube | Materials, surface modification |
| | Lag | Distance between blood-collection space and centrifuge |
| Centrifuge | Tube | Shape, material, surface modification |
| | Rotator | Swing or angle |
| | Centrifugal condition | Force, duration |
| Other handling | Pipetting | Technique, material |
| | Coagulation | $CaCl_2$, thrombin, glassware |

classifying, and applying platelet concentrates. PRP appears to remain the most likely term, given that plasma resuspension of any platelet concentrate is required before application.[1] A high-density fibrin concentrate can facilitate cell migration and the release of cytokines. However, the number of leukocytes affects the concentrate's wound healing ability, leading to the often contradictory results of different studies.

## Standardizing PRP sequestration and application protocols

A rush to standardize PRP protocols could prevent researchers from critical discoveries found only through overcoming clinical obstacles that may defy established norms. For example, a definition of PRP in 2001 proposed an optimal clinical healing concentration of 1,000,000 platelets/μL in a 5-mL volume of plasma for bone.[149] But in 2008, a platelet gel study concluded that a concentration of about $1.5 \times 10^6$ plt/mL appeared to be optimal for proliferation, migration, and invasion of endothelial cells, showing that higher concentrations of growth factors can adversely affect wound healing for soft tissues.[150]

Despite the general similarity in the protocols for preparing PRP, a number of variables affect whole blood centrifugation for platelet concentration and volume: platelet size, anatomical differences of patients, hematocrit variability, the amount and location of autologous blood drawn, the centrifugal forces and number/duration of spins, and temperature variants (including a refrigerated centrifuge; Table 1-1).[151–157]

Compounding the problems of standardization are variations in centrifugation terminology (for example, rotation-per-minute versus g-force), centrifuge rotor radius, patient age and sex,[158] activating or not activating PRP before application,[159,160] using noncommercial PRP kits, needle bore size, and types of anticoagulants or lack thereof.

The variety of methods for delivering PRP to a wound site demonstrates the evolving and sometimes competing techniques for applying PRP and other biologics in wound healing; however, reliable clinical results often require replicable delivery methods in addition to standard production methods. For example, hydrogels, sponges, and nanofiber scaffold fabrication can be used for treating bone defects with PRP.[159]

So clinicians must be wary about too-rigid standardization of the principles and technologies of platelet sequestration, the nomenclature and classification of platelet-rich products, and the application of those products for wound healing. The dynamic and often contradictory nature of PRP derivations and clinical applications across the medical spectrum may in fact represent opportunities for greater scientific and medical understanding and advancement.

## Conclusion

The dental and medical community has traveled a great distance since the mid-1980s when platelets were understood essentially as cells promoting hemostasis. The discovery of growth factors released by platelets introduced regenerative medical therapies that have become the present focus of a great deal of speculation and experimentation in the medical profession.

The succeeding chapters cover both the present and future science of autologous blood concentrates by casting more light than heat on the ongoing conversations concerning standardization and replication of techniques and procedures. It is the author's hope that these chapters will contribute valuable insights concerning biologic/regenerative therapies, helping to remove much of the skepticism regarding the applications of PRP and related autologous products used in a growing number of medical fields, but particularly the fields of oral and maxillofacial surgery, periodontics, dental implants, and facial cosmetic surgery.

## References


1. Marx RE, Garg A. Dental and Craniofacial Applications of Platelet-Rich Plasma. Chicago: Quintessence, 2005.
2. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration. Surgery 1981;90:262–270.
3. Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science 1983;221:1283–1285.
4. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. Oral Surg Oral Med Oral Pathol 1987;64:379–390.
5. Hunt TK. The physiology of wound healing. Ann Emerg Med 1988;17:1265–1273.
6. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg 1990;160:519–524.
7. Davis JC, Hunt TK (eds). Problem Wounds—The Role of Oxygen. New York: Elsevier, 1988.
8. Marx RE, Smith BR. An improved technique for development of the pectoralis major myocutaneous flap. J Oral Maxillofac Surg 1990;48:1168–1180.
9. Cordeiro PG, Disa JJ, Hidalgo DA, Hu QY. Reconstruction of the mandible with osseous free flaps: A 10-year experience with 150 consecutive patients. Plast Reconstr Surg 1999;104:1314–1320.
10. Crowther M, Brown NJ, Bishop ET, Lewis CE. Microenvironmental influence on macrophage regulation of angiogenesis in wounds and malignant tumors. J Leukoc Biol 2001;70:478–490.
11. Moeller BJ, Cao Y, Vujaskovic Z, Li CY, Haroon ZA, Dewhirst MW. The relationship between hypoxia and angiogenesis. Semin Radiat Oncol 2004;14:215–221.
12. Ramakrishnan VR, Yao W, Campana JP. Improved skin paddle survival in pectoralis major myocutaneous flap reconstruction of head and neck defects. Arch Facial Plast Surg 2009;11:306–310.
13. Hunter S, Langemo DK, Anderson J, Hanson D, Thompson P. Hyperbaric oxygen therapy for chronic wounds. Adv Skin Wound Care 2010;23:116–119.
14. Larsson A, Uusijärvi J, Eksborg S, Lindholm P. Tissue oxygenation measured with near infrared spectroscopy during normobaric and hyperbaric oxygen breathing in healthy subjects. Eur J Appl Physiol 2010;109:757–761.
15. Vanni CM, Pinto FR, de Matos LL, de Matos MG, Kanda JL. The subclavicular versus the supraclavicular route for pectoralis major myocutaneous flap: A cadaveric anatomic study. Eur Arch Otorhinolaryngol 2010;267:1141–1146.
16. Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. Br J Dermatol 2010;163:257–268.
17. Knighton DR, Hunt TK, Thakral KK, Goodson WH 3rd. Role of platelets and fibrin in the healing sequence: An in vivo study of angiogenesis and collagen synthesis. Ann Surg 1982;196:379–388.
18. Hunt TK, Knighton DR, Thakral KK, Goodson WH 3rd, Andrews WS. Studies on inflammation and wound healing: Angiogenesis and collagen synthesis stimulated in vivo by resident and activated wound macrophages. Surgery 1984;96:48–54.
19. Dvorak HF, Harvey VS, Estrella P, Brown LF, McDonagh J, Dvorak AM. Fibrin containing gels induce angiogenesis. Implications for tumor stroma generation and wound healing. Lab Invest 1987;57:673–686.
20. Ofosu FA. The blood platelet as a model for regulating blood coagulation on cell surfaces and its consequences. Biochemistry (Mosc) 2002;67:47–55.
21. Nurden AT, Nurden P, Sanchez M, Andia I, Anitua E. Platelets and wound healing. Front Biosci 2008;13:3532–3548.
22. Roy S, Driggs J, Elgharably H, et al. Platelet-rich fibrin matrix improves wound angiogenesis via inducing endothelial cell proliferation. Wound Repair Regen 2011;19:753–766.
23. Malhotra A, Pelletier MH, Yu Y, Walsh WR. Can platelet-rich plasma (PRP) improve bone healing? A comparison between the theory and experimental outcomes. Arch Orthop Trauma Surg 2013;133:153–165.
24. Ross R, Glomset J, Kariya B, Harker L. A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells in vitro. Proc Natl Acad Sci U S A 1974;71:1207–1210.
25. Witte LD, Kaplan KL, Nossel HL, Lages BA, Weiss HJ, Goodman DS. Studies of the release from human platelets of the growth factor for cultured human arterial smooth muscle cells. Circ Res 1978;42:402–409.
26. Ross R, Nist C, Kariya B, Rivest MJ, Raines E, Callis J. Physiological quiescence in plasma-derived serum: Influence of platelet-derived growth factor on cell growth in culture. J Cell Physiol 1978;97(3 pt 2 suppl 1):497–508.
27. Kaplan DR, Chao FC, Stiles CD, Antoniades HN, Scher CD. Platelet alpha granules contain a growth factor for fibroblasts. Blood 1979;53:1043–1052.
28. Assoian RK, Komoriya A, Meyers CA, Miller DM, Sporn MB. Transforming growth factor-beta in human platelets. Identification of a major storage site, purification, and characterization. J Biol Chem 1983;258:7155–7160.
29. Derynck R. Transforming growth factor-alpha: Structure and biological activities. J Cell Biochem 1986;32:293–304.
30. Karey KP, Marquardt H, Sirbasku DA. Human platelet-derived mitogens. I. Identification of insulinlike growth factors I and II by purification and N alpha amino acid sequence analysis. Blood 1989;74:1084–1092.

31. Karey KP, Sirbasku DA. Human platelet-derived mitogens. II. Subcellular localization of insulinlike growth factor I to the alpha-granule and release in response to thrombin. Blood 1989;74:1093–1100.
32. Brunner G, Nguyen H, Gabrilove J, Rifkin DB, Wilson EL. Basic fibroblast growth factor expression in human bone marrow and peripheral blood cells. Blood 1993;81:631–638.
33. Dooley DC, Oppenlander BK, Spurgin P, et al. Basic fibroblast growth factor and epidermal growth factor downmodulate the growth of hematopoietic cells in long-term stromal cultures. J Cell Physiol 1995;165:386–397.
34. Banks RE, Forbes MA, Kinsey SE, et al. Release of the angiogenic cytokine vascular endothelial growth factor (VEGF) from platelets: Significance for VEGF measurements and cancer biology. Br J Cancer 1998;77:956–964.
35. Hormbrey E, Gillespie P, Turner K, et al. A critical review of vascular endothelial growth factor (VEGF) analysis in peripheral blood: Is the current literature meaningful? Clin Exp Metastasis 2002;19:651–663.
36. Sánchez M, Anitua E, Andia I. Poor standardization in platelet-rich therapies hampers advancement. Arthroscopy 2010;26:725–726.
37. Taylor DW, Petrera M, Hendry M, Theodoropoulos JS. A systematic review of the use of platelet-rich plasma in sports medicine as a new treatment for tendon and ligament injuries. Clin J Sport Med 2011;21:344–352.
38. Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev 2014;4:CD010071.
39. Kim TH, Kim SH, Sándor GK, Kim YD. Comparison of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) in rabbit-skull defect healing. Arch Oral Biol 2014;59:550–558.
40. Sandrey MA. Autologous growth factor injections in chronic tendinopathy. J Athl Train 2014;49:428–430.
41. Stellos K, Langer H, Daub K, et al. Platelet-derived stromal cell-derived factor-1 regulates adhesion and promotes differentiation of human CD34+ cells to endothelial progenitor cells. Circulation 2008;117:206–215.
42. Okabe K, Yamada Y, Ito K, Kohgo T, Yoshimi R, Ueda M. Injectable soft-tissue augmentation by tissue engineering and regenerative medicine with human mesenchymal stromal cells, platelet-rich plasma and hyaluronic acid scaffolds. Cytotherapy 2009;11:307–316.
43. Kon E, Filardo G, Di Martino A, Marcacci M. Platelet-rich plasma (PRP) to treat sports injuries: Evidence to support its use. Knee Surg Sports Traumatol Arthrosc 2011;19:516–527.
44. Wu CC, Chen WH, Zao B, et al. Regenerative potentials of platelet-rich plasma enhanced by collagen in retrieving pro-inflammatory cytokine-inhibited chondrogenesis. Biomaterials 2011;32:5847–5854.
45. Bava ED, Barber FA. Platelet-rich plasma products in sports medicine. Phys Sportsmed 2011;39:94–99.
46. Torricelli P, Fini M, Filardo G, et al. Regenerative medicine for the treatment of musculoskeletal overuse injuries in competition horses. Int Orthop 2011;35:1569–1576.
47. Smyth NA, Murawski CD, Fortier LA, Cole BJ, Kennedy JG. Platelet-rich plasma in the pathologic processes of cartilage: Review of basic science evidence. Arthroscopy 2013;29:1399–1409.
48. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638–646.
49. Ono A, Westein E, Hsiao S,et al. Identification of a fibrin-independent platelet contractile mechanism regulating primary hemostasis and thrombus growth. Blood 2008;112:90–99.
50. Cosemans JM, Angelillo-Scherrer A, Mattheij NJ, Heemskerk JW. The effects of arterial flow on platelet activation, thrombus growth, and stabilization. Cardiovasc Res 2013;99:342–352.
51. Karpatkin S. Heterogeneity of human platelets. VI. Correlation of platelet function with platelet volume. Blood 1978;51:307–316.
52. Hartley PS. Platelet senescence and death. Clin Lab 2007;53:157–166.
53. White JG. Electron microscopy methods for studying platelet structure and function. Methods Mol Biol 2004;272:47–63.
54. Coppinger JA, Maguire PB. Insights into the platelet releasate. Curr Pharm Des 2007;13:2640–2646.
55. Bijak M, Saluk J, Ponczek MB, Nowak P, Wachowicz B. The synthesis of proteins in unnucleated blood platelets [in Polish]. Postepy Hig Med Dosw (Online) 2013;67:672–679.
56. Weyrich A, Cipollone F, Mezzetti A, Zimmerman G. Platelets in atherothrombosis: New and evolving roles. Curr Pharm Des 2007;13:1685–1691.
57. Linden MD, Jackson DE. Platelets: Pleiotropic roles in atherogenesis and atherothrombosis. Int J Biochem Cell Biol 2010;42:1762–1766.
58. Schattner M. Platelets and galectins. Ann Transl Med 2014;2:85.
59. Romaniuk MA, Rabinovich GA, Schattner M. Galectins in the regulation of platelet biology. Methods Mol Biol 2015;1207:269–283.
60. Garraud O, Cognasse F. Platelet toll-like receptor expression: The link between "danger" ligands and inflammation. Inflamm Allergy Drug Targets 2010;9:322–333.
61. Nurden AT. Platelets, inflammation and tissue regeneration. Thromb Haemost 2011;105(suppl 1):S13–S33.
62. Goubau C, Buyse GM, Di Michele M, Van Geet C, Freson K. Regulated granule trafficking in platelets and neurons: A common molecular machinery. Eur J Paediatr Neurol 2013;17:117–125.
63. Habets KL, Huizinga TW, Toes RE. Platelets and autoimmunity. Eur J Clin Invest 2013;43:746–757.
64. Koseoglu S, Flaumenhaft R. Advances in platelet granule biology. Curr Opin Hematol 2013;20:464–471.
65. Golebiewska EM, Poole AW. Platelet secretion: From haemostasis to wound healing and beyond. Blood Rev 2015;29:153–162.
66. Duchene J, von Hundelshausen P. Platelet-derived chemokines in atherosclerosis. Hamostaseologie 2015;35:137–141.
67. van den Dolder J, Mooren R, Vloon AP, Stoelinga PJ, Jansen JA. Platelet-rich plasma: Quantification of growth factor levels and the effect on growth and differentiation of rat bone marrow cells. Tissue Eng 2006;12:3067–3073.
68. Nikolidakis D, Jansen JA. The biology of platelet-rich plasma and its application in oral surgery: Literature review. Tissue Eng Part B Rev 2008;14:249–258.
69. Lubkowska A, Dolegowska B, Banfi G. Growth factor content in PRP and their applicability in medicine. J Biol Regul Homeost Agents 2012;26(2 suppl 1):3S–22S.
70. Uutela M, Wirzenius M, Paavonen K, et al. PDGF-D induces macrophage recruitment, increased interstitial pressure, and blood vessel maturation during angiogenesis. Blood 2004;104:3198–3204.
71. Everts PA, Knape JT, Weibrich G, et al. Platelet-rich plasma and platelet gel: A review. J Extra Corpor Technol 2006;38:174–187.
72. Appelmann I, Liersch R, Kessler T, Mesters RM, Berdel WE. Angiogenesis inhibition in cancer therapy: Platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) and their receptors. Biological functions and role in malignancy. Recent Results Cancer Res 2010;180:51–81.
73. Caplan AI. Mesenchymal stem cells and gene therapy. Clin Orthop Relat Res 2000;(379 suppl):S67–S70.
74. Tocci A, Forte L. Mesenchymal stem cell: Use and perspectives. Hematol J 2003;4:92–96.
75. Reiser J, Zhang XY, Hemenway CS, Mondal D, Pradhan L, La Russa VF. Potential of mesenchymal stem cells in gene therapy approaches for inherited and acquired diseases. Expert Opin Biol Ther 2005;5:1571–1584.

76. Ye JS, Su XS, Stoltz JF, de Isla N, Zhang L. Signaling pathways involved in the process of mesenchymal stem cells differentiating into hepatocytes. Cell Prolif 2015;48:157–165.
77. Ball SG, Shuttleworth CA, Kielty CM. Mesenchymal stem cells and neovascularization: Role of platelet-derived growth factor receptors. J Cell Mol Med 2007;11:1012–1030.
78. Graham S, Leonidou A, Lester M, Heliotis M, Mantalaris A, Tsiridis E. Investigating the role of PDGF as a potential drug therapy in bone formation and fracture healing. Expert Opin Investig Drugs 2009;18:1633–1654.
79. Hellberg C, Ostman A, Heldin CH. PDGF and vessel maturation. Recent Results Cancer Res 2010;180:103–114.
80. Javed F, Al-Askar M, Al-Rasheed A, Al-Hezaimi K. Significance of the platelet-derived growth factor in periodontal tissue regeneration. Arch Oral Biol 2011;56:1476–1484.
81. Donovan J, Abraham D, Norman J. Platelet-derived growth factor signaling in mesenchymal cells. Front Biosci (Landmark Ed) 2013;18:106–119.
82. Iwayama T, Olson LE. Involvement of PDGF in fibrosis and scleroderma: Recent insights from animal models and potential therapeutic opportunities. Curr Rheumatol Rep 2013;15:304.
83. Shah P, Keppler L, Rutkowski J. A review of platelet derived growth factor playing pivotal role in bone regeneration. J Oral Implantol 2014;40:330–340.
84. Finnson KW, McLean S, Di Guglielmo GM, Philip A. Dynamics of transforming growth factor beta signaling in wound healing and scarring. Adv Wound Care (New Rochelle) 2013;2:195–214.
85. Pakyari M, Farrokhi A, Maharlooei MK, Ghahary A. Critical role of transforming growth factor beta in different phases of wound healing. Adv Wound Care (New Rochelle) 2013;2:215–224.
86. Ferguson MW, O'Kane S. Scar-free healing: From embryonic mechanisms to adult therapeutic intervention. Philos Trans R Soc Lond B Biol Sci 2004;359:839–850.
87. Bachem MG, Zhou Z, Zhou S, Siech M. Role of stellate cells in pancreatic fibrogenesis associated with acute and chronic pancreatitis. J Gastroenterol Hepatol 2006;21(suppl 3):S92–S96.
88. Occleston NL, Laverty HG, O'Kane S, Ferguson MW. Prevention and reduction of scarring in the skin by transforming growth factor beta 3 (TGFbeta3): From laboratory discovery to clinical pharmaceutical. J Biomater Sci Polym Ed 2008;19:1047–1063.
89. Lo DD, Zimmermann AS, Nauta A, Longaker MT, Lorenz HP. Scarless fetal skin wound healing update. Birth Defects Res C Embryo Today 2012;96:237–247.
90. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen 2008;16:585–601.
91. Yang B, Zhou L, Peng B, Sun Z, Dai Y, Zheng J. In vitro comparative evaluation of recombinant growth factors for tissue engineering of bladder in patients with neurogenic bladder. J Surg Res 2014;186:63–72.
92. Song F, Tang J, Geng R, et al. Comparison of the efficacy of bone marrow mononuclear cells and bone mesenchymal stem cells in the treatment of osteoarthritis in a sheep model. Int J Clin Exp Pathol 2014;7:1415–1426.
93. Mariani E, Pulsatelli L, Facchini A. Signaling pathways in cartilage repair. Int J Mol Sci 2014;15:8667–8698.
94. Mammoto T, Jiang A, Jiang E, Mammoto A. Platelet rich plasma extract promotes angiogenesis through the angiopoietin1-Tie2 pathway. Microvasc Res 2013;89:15–24.
95. Jeong DU, Lee CR, Lee JH, et al. Clinical applications of platelet-rich plasma in patellar tendinopathy. Biomed Res Int 2014;2014:249498.
96. Franceschi RT. Biological approaches to bone regeneration by gene therapy. J Dent Res 2005;84:1093–1103.
97. Wang Y, Nishida S, Sakata T, et al. Insulin-like growth factor-I is essential for embryonic bone development. Endocrinology 2006;147:4753–4761.
98. Sroga GE, Wu PC, Vashishth D. Insulin-like growth factor 1, glycation and bone fragility: Implications for fracture resistance of bone. PLoS One 2015;10:e0117046.
99. Omori E, Inagaki M, Mishina Y, Matsumoto K, Ninomiya-Tsuji J. Epithelial transforming growth factor β-activated kinase 1 (TAK1) is activated through two independent mechanisms and regulates reactive oxygen species. Proc Natl Acad Sci U S A 2012;109:3365–3370.
100. Stratman AN, Davis GE. Endothelial cell-pericyte interactions stimulate basement membrane matrix assembly: Influence on vascular tube remodeling, maturation, and stabilization. Microsc Microanal 2012;18:68–80.
101. Marx RE. Platelet-rich plasma: Evidence to support its use. J Oral Maxillofac Surg 2004;62:489–496.
102. Hallman M, Thor A. Bone substitutes and growth factors as an alternative/complement to autogenous bone for grafting in implant dentistry. Periodontol 2000 2008;47:172–192.
103. Akhundov K, Pietramaggiori G, Waselle L, et al. Development of a cost-effective method for platelet-rich plasma (PRP) preparation for topical wound healing. Ann Burns Fire Disasters 2012;25:207–213.
104. Pietrzak WS, Eppley BL. Platelet rich plasma: Biology and new technology. J Craniofac Surg 2005;16:1043–1054.
105. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: A review of biology and applications in plastic surgery. Plast Reconstr Surg 2006;118:147e–159e.
106. Rodrigues SV, Acharya AB, Thakur SL. Platelet-rich plasma. A review. N Y State Dent J 2012;78:26–30.
107. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med 2003;33:381–394.
108. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: A review of the literature. J Bone Joint Surg Br 2009;91:987–996.
109. Carless PA, Rubens FD, Anthony DM, O'Connell D, Henry DA. Platelet-rich-plasmapheresis for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;(3):CD004172.
110. Vu TD, Pal SN, Ti LK, et al. An autologous platelet-rich plasma hydrogel compound restores left ventricular structure, function and ameliorates adverse remodeling in a minimally invasive large animal myocardial restoration model: A translational approach: Vu and Pal "Myocardial Repair: PRP, Hydrogel and Supplements." Biomaterials 2015;45:27–35.
111. Drago L, Bortolin M, Vassena C, Taschieri S, Del Fabbro M. Antimicrobial activity of pure platelet-rich plasma against microorganisms isolated from oral cavity. BMC Microbiol 2013;13:47.
112. Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am J Sports Med 2007;35:245–251.
113. Randelli PS, Arrigoni P, Cabitza P, Volpi P, Maffulli N. Autologous platelet rich plasma for arthroscopic rotator cuff repair. A pilot study. Disabil Rehabil 2008;30:1584–1589.
114. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: A systematic review with quantitative synthesis. Arthroscopy 2012;28:1718–1727.
115. Charousset C, Zaoui A, Bellaïche L, Piterman M. Does autologous leukocyte-platelet-rich plasma improve tendon healing in arthroscopic repair of large or massive rotator cuff tears? Arthroscopy 2014;30:428–435.
116. Bennett SP, Griffiths GD, Schor AM, Leese GP, Schor SL. Growth factors in the treatment of diabetic foot ulcers. Br J Surg 2003;90:133–146.

117. Kirsner RS, Warriner R, Michela M, Stasik L, Freeman K. Advanced biological therapies for diabetic foot ulcers. Arch Dermatol 2010;146:857–862.
118. Gawdat HI, Hegazy RA, Fawzy MM, Fathy M. Autologous platelet rich plasma: Topical versus intradermal after fractional ablative carbon dioxide laser treatment of atrophic acne scars. Dermatol Surg 2014;40:152–161 [erratum 2014;40:601].
119. Assenza M, Valesini L, Monacelli G, et al. Traumatic complex wounds, multidisciplinary approach: Our experience in a case series. Clin Ter 2010;161:e95–e99.
120. Serra R, Buffone G, Dominijanni A, Molinari V, Montemurro R, de Franciscis S. Application of platelet-rich gel to enhance healing of transmetatarsal amputations in diabetic dysvascular patients. Int Wound J 2013;10:612–615.
121. Yamada T, Onishi K, Utsunomiya M, Nakamura M. Our treatment strategy for critical limb ischemia. Int J Vasc Med 2013;2013:437471.
122. Toscano N, Holtzclaw D. Surgical considerations in the use of platelet-rich plasma. Compend Contin Educ Dent 2008;29:182–185.
123. Smith SE, Roukis TS. Bone and wound healing augmentation with platelet-rich plasma. Clin Podiatr Med Surg 2009;26:559–588.
124. Maney P, Amornporncharoen M, Palaiologou A. Applications of plasma rich in growth factors (PRGF) in dental surgery: A review. J West Soc Periodontol Periodontal Abstr 2013;61:99–104.
125. Lowery GL, Kulkarni S, Pennisi AE. Use of autologous growth factors in lumbar spinal fusion. Bone 1999;25(2 suppl):47S–50S.
126. Jenis LG, Banco RJ, Kwon B. A prospective study of autologous growth factors (AGF) in lumbar interbody fusion. Spine J 2006;6:14–20.
127. Dimar JR 2nd, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. J Bone Joint Surg Am 2009;91:1377–1386.
128. Zhang H, Wang F, Ding L, et al. A meta-analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous iliac crest bone graft. PLoS One 2014;9:e97049.
129. Kitoh H, Kitakoji T, Tsuchiya H, Katoh M, Ishiguro N. Distraction osteogenesis of the lower extremity in patients with achondroplasia/hypochondroplasia treated with transplantation of culture-expanded bone marrow cells and platelet-rich plasma. J Pediatr Orthop 2007;27:629–634.
130. Kitoh H, Kawasumi M, Kaneko H, Ishiguro N. Differential effects of culture-expanded bone marrow cells on the regeneration of bone between the femoral and the tibial lengthenings. J Pediatr Orthop 2009;29:643–649.
131. Kim SJ, Pierce W, Sabharwal S. The etiology of short stature affects the clinical outcome of lower limb lengthening using external fixation. A systematic review of 18 trials involving 547 patients. Acta Orthop 2014;85:181–186.
132. Weibrich G, Kleis WK, Hitzler WE, Hafner G. Comparison of the platelet concentrate collection system with the plasma-rich-in-growth-factors kit to produce platelet-rich plasma: A technical report. Int J Oral Maxillofac Implants 2005;20:118–123.
133. Gandhi A, Bibbo C, Pinzur M, Lin SS. The role of platelet-rich plasma in foot and ankle surgery. Foot Ankle Clin 2005;10:621–637.
134. Bibbo C, Hatfield PS. Platelet-rich plasma concentrate to augment bone fusion. Foot Ankle Clin 2010;15:641–649.
135. Bielecki T, Gazdzik TS, Szczepanski T. Benefit of percutaneous injection of autologous platelet-leukocyte-rich gel in patients with delayed union and nonunion. Eur Surg Res 2008;40:289–296.
136. Nathan ST, Fisher BE, Roberts CS, Giannoudis PV. The management of nonunion and delayed union of patella fractures: A systematic review of the literature. Int Orthop 2011;35:791–795.
137. Del Corso M, Vervelle A, Simonpieri A, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 1: Periodontal and dentoalveolar surgery. Curr Pharm Biotechnol 2012;13:1207–1230.
138. Simonpieri A, Del Corso M, Vervelle A, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: Bone graft, implant and reconstructive surgery. Curr Pharm Biotechnol 2012;13:1231–1256.
139. Roffi A, Filardo G, Kon E, Marcacci M. Does PRP enhance bone integration with grafts, graft substitutes, or implants? A systematic review. BMC Musculoskelet Disord 2013;14:330.
140. Georgakopoulos I, Tsantis S, Georgakopoulos P, et al. The impact of platelet rich plasma (PRP) in osseointegration of oral implants in dental panoramic radiography: Texture based evaluation. Clin Cases Miner Bone Metab 2014;11:59–66.
141. Davis VL, Abukabda AB, Radio NM, et al. Platelet-rich preparations to improve healing. Part I: Workable options for every size practice. J Oral Implantol 2014;40:500–510.
142. Schwartz-Arad D, Ofec R, Eliyahu G, Ruban A, Sterer N. Long-term follow-up of dental implants placed in autologous onlay bone graft. Clin Implant Dent Relat Res 2016;18:449–461.
143. Ntounis A, Geurs N, Vassilopoulos P, Reddy M. Clinical assessment of bone quality of human extraction sockets after conversion with growth factors. Int J Oral Maxillofac Implants 2015;30:196–201.
144. Grant WP, Jerlin EA, Pietrzak WS, Tam HS. The utilization of autologous growth factors for the facilitation of fusion in complex neuropathic fractures in the diabetic population. Clin Podiatr Med Surg 2005;22:561–584.
145. Sood A, Cunningham C, Lin S. The BB Wistar rat as a diabetic model for fracture healing. ISRN Endocrinol 2013;2013:349604.
146. Chahla J, Cimque ME, Piuzzi NS, et al. A call for standardization in platelet-rich plasmapreparation protocols and composition reporting. A systematic review of the clinical orthopaedic literature. J Bone Joint Surg Am 2017;99:1769–1779.
147. Mautner K, Malanga GA, Smith J, et al. A call for a standard classification system for future biologic research: The rationale for new PRP nomenclature. Phys Med Rehabil 2015;7(4 suppl):S53–S59.
148. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 2009;27:158–167.
149. Marx RE. Platelet-rich plasma (PRP): What is PRP and what is not PRP? Implant Dent 2001;10:225–228.
150. Rughetti A, Giusti I, D'Ascenzo S, et al. Platelet gel-released supernatant modulates the angiogenic capability of human endothelial cells. Blood Transfus 2008;6:12–17.
151. Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: A review and author's perspective. J Cutan Aesthet Surg 2014;7:189–197.
152. Anitua E, Aguirre JJ, Algorta J, et al. Effectiveness of autologous preparation rich in growth factors for the treatment of chronic cutaneous ulcers. J Biomed Mater Res B Appl Biomater 2008;84:415–421.
153. Mazzocca AD, McCarthy MB, Chowaniec DM, et al. Platelet-rich plasma differs according to preparation method and human variability. J Bone Joint Surg Am 2012;94:308–316.
154. Araki J, Jona M, Eto H, et al. Optimized preparation method of platelet-concentrated plasma and noncoagulating platelet-derived factor concentrates: maximization of platelet concentration and removal of fibrinogen. Tissue Eng Part C Methods 2012;18:176–185.
155. Bausset O, Giraudo L, Veran J, et al. Formulation and storage of platelet-rich plasma homemade product. Biores Open Access 2012;1:115–123.

156. Amable PR, Carias RB, Teixeira MV, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther 2013;4:67.
157. Kececi Y, Ozsu S, Bilgir O. A cost-effective method for obtaining standard platelet-rich plasma. Wounds 2014;26:232–238.
158. Evanson JR, Guyton MK, Oliver DL, et al. Gender and age differences in growth factor concentrations from platelet-rich plasma in adults. Mil Med 2014;179:799–805.
159. Bowlin GL, Sell SA. Platelet-rich plasma in bone regeneration: Engineering the delivery for improved clinical efficacy. Biomed Res Int 2014;2014:392398.
160. Han B, Woodell-May J, Ponticiello M, Yang Z, Nimni M. The effect of thrombin activation of platelet-rich plasma on demineralized bone matrix osteoinductivity. J Bone Joint Surg Am 2009;91:1459–1470.

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