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Review

Advancements in Regenerative Medicine for Aesthetic Dermatology: A Comprehensive Review and Future Trends

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Abstract: The growing interest in maintaining a youthful appearance has encouraged an accelerated development of innovative, minimally invasive aesthetic treatments for facial rejuvenation and regeneration. The close correlation between tissue repair, regeneration, and aging has paved the way for the application of regenerative medicine principles in cosmetic dermatology. The theoretical substrates of regenerative medicine applications in dermo-aesthetics are plentiful. However, regenerative dermatology is an emerging field and needs more data and in vivo trials to reach a consensus on the standardization of methods. In this review, we summarize the principles of regenerative medicine and techniques as they apply to cosmetic dermatology, suggesting unexplored fields and future directions.

Keywords: skin rejuvenation; skin quality; aesthetic dermatology; pre-juvenation

Citation: Trovato, F.; Ceccarelli, S.; Michelini, S.; Vespasiani, G.; Guida, S.; Galadari, H.I.; Nisticò, S.P.; Colonna, L.; Pellacani, G. Advancements in Regenerative Medicine for Aesthetic Dermatology: A Comprehensive Review and Future Trends. *Cosmetics* **2024**, *11*, 49. https://doi.org/10.3390/cosmetics11020049

Academic Editor: Danuta Nowicka

Received: 4 February 2024
Revised: 10 March 2024
Accepted: 14 March 2024
Published: 31 March 2024

1. Introduction

The growing interest in maintaining a youthful and rested appearance has prompted an accelerated development of noninvasive and minimally invasive aesthetic approaches for skin rejuvenation and regeneration. The population requiring mini-invasive aesthetic treatments is continuously expanding, extending beyond the traditional limits of the over-45s to also millennials (born ~1981 to 1996) and even Generation Z (born ~from 1997), in the context of pre-rejuvenation [1–3]. The term "pre-juvenation" refers to a preventive approach of anti-aging procedures that emerged in the early 2000s between millennials and Generation Z (Gen Z) [2]. Since then, it has become a trending topic across all media platforms and serves as a driving force behind the growing demand of noninvasive treatments in aesthetics [4]. This innovative field sprouts regenerative dermatology as a combination of the principles of regenerative medicine in the context of skin regeneration and rejuvenation. The close correlation between tissue repair, regeneration, and aging [5–7] underlies the rationale for the application of regenerative medicine in aesthetic dermatology. Regenerative medicine aims to replace lost or damaged tissues, while regenerative aesthetics focuses on regenerating soft tissues lost or damaged due to aging processes [8].

2. Principles of Regenerative Medicine

The skin shows its regenerative ability mostly during the complex process of wound healing. Following skin trauma, a network of events is launched that involves three steps:

the early coagulation and hemostasis phase, inflammatory phase, and growth phase [9]. (Figure 1) The initial response to a wound is the constriction of injured blood vessels and activation of platelets to form a fibrin clot. Platelets are anucleate cells derived from megakaryocytes [10]. They contain secretory granules; among them, α-granules are the most abundant [11,12] and are released immediately after the platelets' activation. With α-granules, numerous active factors are secreted: platelet-derived growth factor (PDGF), transforming growth factor (TGF), platelet factor interleukin (IL), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor IGF, adhesive proteins (vWF, TSP1, and vitronectin), coagulation factors (factors V, VII, XI, and XIII), protease inhibitors (protein C, PAI-1, and TFPI), and fibronectin [13–15]. Growth factors account for various functions, including promoting mitogenesis and the differentiation of stem cells, fibroblasts, keratinocytes, and endothelial cells. They induce cell proliferation, chemotaxis, and angiogenesis, promoting cell differentiation, proliferation, and regeneration [16]. The fibrin clot made by platelets interrupts blood flow and provides a structure for incoming inflammatory cells, including neutrophils, monocytes, Langerhans cells, dermal dendritic cells, and T lymphocytes. When inflammation ends, the growth phase begins with angiogenesis, which involves the proliferation, migration, and branching of endothelial cells [17]. The formation of new blood vessels is a key step in wound healing. The activation of endothelial cells requires growth factors from contiguous cells (from platelets, keratinocytes, macrophages, and subcutaneous adipose tissue) [18]. Endothelial cells branch out to form new capillaries in response to pro-angiogenic, hypoxia-responsive signals, such as VEGF, FGF, PDGF-B, TGF-β, and angiopoietins [17–19]. Activated endothelial cells express the surface markers' intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, E-selectin, and P-selectin, which contribute to intercellular and leukocyte interactions. Pro-angiogenic macrophages release growth factors for endothelial cell proliferation while fusing newly formed capillaries [17]. A major hallmark of the proliferative phase of wound healing is wound contraction, in which collagen fibrils are organized to increase the strength of the tissue. Fibroblasts infiltrate and degrade the fibrin clot producing various matrix metalloproteinases (MMPs) and replace it with extracellular matrix (ECM) components, such as collagen I–IV and XVIII, glycoproteins, proteoglycans, laminin, thrombospondin, glycosaminoglycans (GAGs), hyaluronic acid (HA), and heparan sulfate [20,21]. Fibroblasts exhibit great heterogeneity based on tissue origin and activation state, leading to different functions in the wound healing process. Studies on fibroblast subpopulations reveal that fibroblasts comprise distinct lineages and return different signals to nearby cells in the skin; this affects dermo-epidermal interactions during wound healing. Dermal papilla fibroblasts play a key role in Wnt/β-catenin signaling in hair follicle development [22]. The inhibition of β-catenin by fibroblasts promotes hair follicle regeneration, while its activation diminishes it [23]. Conversely, epidermal stem cells of the follicular bulge are capable of inducing differentiation into myofibroblasts and smooth muscle cells by sending signals to dermal papilla fibroblasts [24,25]. Myofibroblasts are α-SMA-positive transient cells that derive from activated fibroblasts and play a pivotal role in wound contraction. During mechanical stress, fibroblasts from the dermis and subcutaneous tissue initially transition to proto-myofibroblasts, expressing β- and γ-cytoplasmic actin [20,26]. The interaction of proto-myofibroblasts with fibronectin and stimulation by TGF-β induce differentiation into myofibroblasts that synthesize α-Smooth Cell Actin (α-SMA), [15,27] and produce ECM proteins, including collagen types I and III [28]. Myofibroblasts deposit ECM and show characteristics of contractile smooth muscle cells. Plikus M.V. et al. demonstrated that in murine prototypes, myofibroblasts of early formed hair follicles can form dermal adipocytes following injury and that this transition reduces scar formation [29,30]. Additional ECM components, such as hyaluronic acid, osteopontin, periostin, vitronectin, endothelin, angiotensin, CCN2, and Cx43, are associated with differentiation to myofibroblasts [31–34]. PDGF is linked to proto-myofibroblast motility [35] and matrix metalloproteinases (MMPs) show that they mediate myofibroblast differentiation, but the exact mechanism remains

unknown [36]. Some inflammatory mediators, including TNF-α, can also inhibit differentiation [37]. Shook et al., among others, revealed that myofibroblast transition and dermal adipocytes lipolysis are necessary to initiate inflammation after injury and promote wound repair [38]. Sun et al. studied the interactions between the IL-1 and WNT pathways in the regulation of dermal adipocyte lineage cells during skin development and wound regeneration. They defined the various characteristics of dermal adipocytes in developing or injured mouse skin and revealed that dermal adipogenesis and lipolysis are regulated by an antagonistic interaction between the IL-1-pCREB and WNT-β catenin pathways [39]. During the wound healing, adipocytes cleave triglycerides to promptly release fatty acids to support the metabolism of the surrounding tissues. Adipocyte lipolysis begins with the activation of adipose triglyceride lipase (ATGL), which releases free fatty acid (FFA) and diacylglycerol [40,41]. Subsequent lipases catalyze the hydrolysis of the remaining fatty acids. Shook et al. found that before macrophage infiltration, mature adipocytes undergo lipolysis, releasing FAs into skin wounds [38]. Chang et al. analyzed the function of the long non-coding lncRNA FOXD2-AS1 in ASCs-exos to find if highly expressed lncRNA FOXD2-AS1 in ASCs-derived exosomes affects immortal aneuploid keratinocytes (HaCaT) cells via regulating the miR-185-5p/ROCK2 axis. The study revealed that upregulation of the lncRNA FOXD2-AS1 in exosomes derived from ASCs could enhance the migration and proliferation of HaCaT cells by regulating the miR-185-5p/ROCK2 axis [42]. This evidence makes adipocytes, fibroblasts, and platelets the key cells in the skin regeneration process [14,20,21,38].

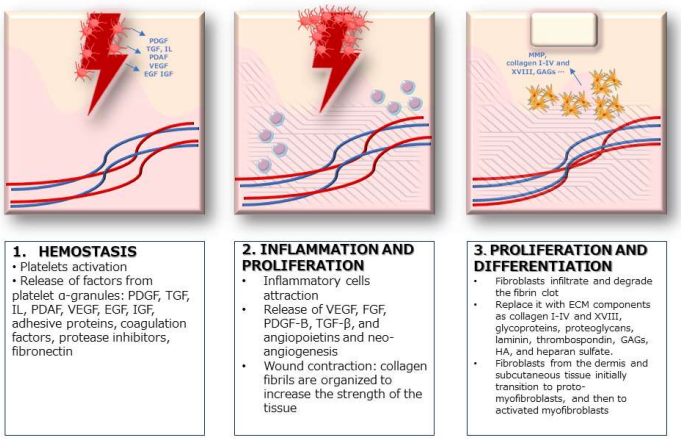

Figure 1. Stages of wound healing.

3. Regenerative Approaches in Aesthetic Dermatology

Regenerative medicine and even more its application in aesthetic dermatology are recent findings in medical practice. Misha et al. defined three pillars of regenerative medicine, translated into the field of dermo-aesthetics: cells and cell derivatives, Biochemical Cues (Bio-Cues), and scaffolds [43]. (Table 1)The use of stem cells and tissue fractions, first established in the surgical field, is also making its way into the dermo-aesthetic field with nanofat grafting [44,45]. The Bio-Cues represent therapeutic approaches that improve the tissue microenvironment through cell signaling. They include growth factors and derivatives (e.g., platelet-rich plasma and platelet-rich fibrin [13,46]), small bioactive molecules, and extracellular vesicles (EVs) [47–49]. The ease of execution and the supporting evidence in the literature made them increasingly more popular [47]. The Aesthetic Regenerative Scaffolds (ARSs) are injectable biomaterials that inhibit a chronic inflammatory response, reverting fibrosis and enhancing physiological tissue regeneration [50,51]. They include Calcium Hydroxyapatite (CaHA), Hyaluronic Acid (HA), and Poli-L-Lactic Acid (PLLA) dermal fillers [50,52–54].

Table 1. Pillars of regenerative medicine in dermo-aesthetics.

Regenerative Approaches		Mechanism of Action
Cells and cell derivatives	Adipose-derived Stem Cells (ASCs) Nanofat Grafting	Adipose stem cells maintain the dermo-epidermal structure and show paracrine capabilities [55].
Biochemical Cues (Bio-Cues)	Platelet-Rich Plasma (PRP) Platelet-Rich Fibrin (FRP) Extracellular Vesicles (EVs)	Improve the tissue microenvironment through cell signaling [11,56].
Aesthetic Regenerative Scaffolds (ARSs)	Calcium Hydroxyapatite (CaHA) Hyaluronic Acid (HA) Poli-L-Lactic Acid (PLLA)	Injectable biomaterials that inhibit chronic inflammatory response, reverting fibrosis and enhancing physiological tissue regeneration [53,54,57].

3.1. Adipose-Derived Stem Cells (ASCs) and Nanofat Grafting

Adipose tissue represents a rich deposit of adipose-derived mesenchymal stem cells (ASCs), which compose a heterogenic population of multipotent progenitors [55,58]. ASCs reside in "stem cell niches" of adipose tissue, where they are closely interconnected with the ECM and other supporting cells [59,60]. Several studies have proven that the niche acts as a modulator of the biological properties and the ability of ASCs to proliferate, differentiate, and migrate in the context of cellular regeneration and wound healing [61–63]. ASCs' secretome represents a topic of great interest in regenerative medicine, because ASCs produce several molecules involved in cell-to-cell signaling, such as inflammatory, immuno-modulatory, and angiogenic cytokines (IL-6 IL-7, IL-8, IL-11, and TNFa) [64–66], growth factors (HGF and VEGF) [64,67], and chemokines [64]. In the context of skin regeneration, ASCs act as paracrine actors, [68,69] playing a pivotal role in maintaining the dermo-epidermal structure, as a physiological response to local damage [70]. It has been shown that ASCs can differentiate into keratinocytes, dermal fibroblasts (DFs), and other skin components [70,71]. Autologous fat grafting is considered the filler *par excellence* because it possesses unique characteristics: biocompatibility, versatility, long-lasting effects, and natural appearance [72]. Since the dawn of its use for soft tissue augmentation by Neuber in 1893, the potential of lipofilling has been recognized, and today it emerges as a key technique in several areas of plastic surgery, such as facelift surgery, breast augmentation, and reconstructive surgery in wound healing [73–77]. Within the area of non-invasive cosmetic procedures comes nanofat grafting, first described in 2013 by Tonnard and colleagues, [44,72], that has gained popularity in cosmetic surgery in recent years [78]. It involves the injection of a highly concentrated solution of autologous progenitor cells, without viable adipocytes [72]. The protocol consists of emulsifying and filtering the microfat harvested by liposuction [79]. A whitish fluid rich in mesenchymal stem cells is obtained, with 25% adipocytes and a 75% stromal vascular fraction (SVF), containing ASCs, ECs, monocytes and macrophages, granulocytes, and lymphocytes [72]. Nanofat is injected intradermally using a retrograde, fan-shaped technique. Nanofat is approximately 400 to 600 µm [80]. Typically, 1 mL of nanofat can cover an area of 1 cm by 1 cm. It can also be delivered by microneedling [44,72]. (Figure 2) Nanofat shows few-to-any filling characteristics, so its field of action includes skin rejuvenation and skin quality by injecting regenerative cells and ECM elements [72]. Menkes et al. evaluate the regenerative and face-lifting effects of nanofat grafting, enrolling 50 patients and treating them with subcutaneous injections of 18 mL of nanofat-PRP. Improved skin quality and a lifting effect were observed at 2–4 weeks, with maintenance of the results up to 6 months after treatment. Biopsies showed an increase in dermal cellularity, vascular density, elastic fiber, and collagen density [81]. Kadry et al. compared the efficacy of PRP versus combined fat transfer and nanofat by treating 30 patients with infraorbital dark circles. Autologous fat transfer with nanofat was shown to be significantly superior to PRP in improvement and satisfaction. In total, 73.7% of patients treated with combined fat transfer and nanofat and 33% of the PRP group showed an excellent and a moderate response in terms of improvement and patients' satisfaction. Non-responders were significantly higher in

the PRP group (53.3% vs. 6.5%) [82]. Nilforoushzadehet al. conducted a study on nine adult patients with atrophic acne scars on the face to investigate the effectiveness of a combined treatment with autologous fat transplantation, SVF cells, and PRP as the cell therapy techniques on atrophic acne scars. The study showed significant improvement in skin pores, blemishes, skin brightness and melanin content, skin elasticity, and TEWL (transepidermal water loss) after 6 months of treatment. In addition, denser skin layers were observed in both the epidermis and dermis. In total, 66.6% of patients showed good satisfaction after treatment [83]. Nanofat grafting is a promising and theoretically attractive option because it looks more "natural" to the patient than other injectables and can produce long-term results. ASCs' secretome also showed the ability to modulate multiple targets simultaneously, becoming the subject of clinical and preclinical studies on the management of dermatological conditions, such as atopic dermatitis (AD), vitiligo, psoriasis, acne, lichen sclerosus (LS), chronic wounds, and alopecia [84]. However, when considering potential disadvantages, the following should be mentioned: donor site morbidity, unpredictability of graft survival, [85,86] graft hypertrophy, and exposure to local or general anesthesia [87].

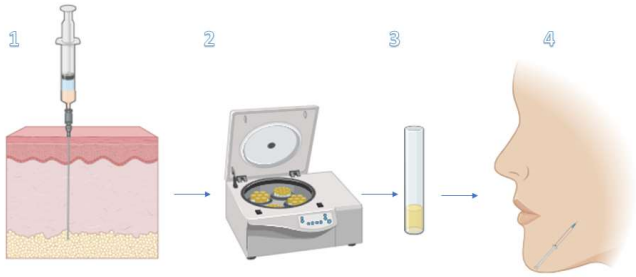

Figure 2. Nanofat grafting process. 1. Harvest microfat by liposuction 2. Emulsify and filter it. 3. Fluid rich in mesenchymal stem cells is obtained, with 25% adipocytes and 75% SVF (ASCs, ECs, monocytes and macrophages, granulocytes, and lymphocytes). 4. Intradermic injection of nanofat [88].

3.2. Biochemical Cues (Bio-Cues)—Platelet-Rich Plasma (PRP), Platelet-Rich Fibrin (FRP), and Extracellular Vescicles (EVs)

Platelet concentrates are processed blood extracts obtained mostly by centrifugation [89]. Depending on the content of leukocytes and fibrin, they are classified into four groups: pure platelet-rich plasma (PRP), leukocyte-rich and platelet-rich plasma (LPRP), pure platelet-rich fibrin (PRF), and leukocyte-rich and platelet-rich fibrin (L-PRF) [90,91]. Platelet-rich plasma (PRP) is defined as the concentration and collection of autologous platelet-rich plasma by centrifugation (Figure 3). Platelet-rich fibrin (PRF) represents a new-generation platelet concentrate with simplified preparation without the biochemical manipulation of blood [8,46]. Both preparations contain significant concentrations of VEGF, EGF, PDGF, TGF-B, and adhesive proteins, such as fibrin and fibronectin [13,46,92]. The exact mechanism of action of PRP in rejuvenation is still unclear, but it is thought that an injection of PRP can induce tissue repair, through the release of biologically active factors and adhesion proteins, with the initiation of tissue regeneration: hemostatic cascade, synthesis of new connective tissue, and angiogenesis [92,93]. It has been hypothesized that locally released growth factors and cytokines contribute to tissue repair through paracrine and autocrine mechanisms at all stages of the tissue repair process [94]. Su et al. suggested the negative regulation of JAK/STAT activation by PRP, pre-treating a skin flap ischemia–reperfusion injury murine model with PRP. PRP was found to protect against flap injury by improving survival, blood perfusion, and angiogenesis; reducing oxidative stress and inflammation; and attenuating apoptosis, in part through the inactivation of the JAK/STAT signaling pathway [95]. PRP is currently used both topically and intradermally. Despite the availability of different procedures for PRP extraction and on the large-scale use of PRP in aesthetics, there is no consensus regarding either the mode of extraction or the administration of the product [93,96,97]. Even the terminology itself is

lacking standardization, leading to confusion [98]. The lack of consensus and standardization has not stopped the use of PRP from growing in popularity and widespread use in various medical fields. Xiao et al.'s systematic review of 44 studies on the use of PRP for facial rejuvenation showed beneficial effects both in monotherapy and in combination (e.g., laser, fat grafting, subcision, growth factors, and thread lifting), revealing the high regenerative potential of PRP [93]. Trink et al. conducted a randomized, double-blind study on 45 patients to evaluate the effects of PRP on alopecia areata (AA). PRP achieved better results to Triamcinolone and Placebo in terms of an increase in hair regrowth, a decrease in dystrophic hair number, and a reduction in burning or itching sensation. The Ki-67 levels were significantly higher with PRP, indicating increased cell proliferation [99]. Mahmoodabadi et al. injected the PRF matrix into the subcutis in the periorbital areas of 15 patients over the age of 30. The results showed significant improvement in deep, fine, and small wrinkles; periocular hyperpigmentation; and overall skin appearance in the treated area [100]. PRF is widely used in dental and bone grafting procedures, but it is rapidly gaining ground in the fields of cosmetic dermatology and wound healing. Shashank et al. reported four representative cases in which injectable PRF (iPRF) has proven to be useful in the treatment of androgenetic alopecia, rejuvenation of the under-eye area, temporary correction of facial skin folds, and healing of difficult-to-treat wounds and ulcers [101]. Extracellular vesicles (EVs) are defined as membrane structures released by cells and include two main types, exosomes and microvesicles (MVs) [56]. EVs are fundamental components of cell–cell communication, carrying transport proteins, nucleic acids, and lipids. They have been reported to mediate many cellular processes, such as proliferation, differentiation, and cell migration [102,103]. The regenerative properties of EVs have been demonstrated on a large variety of degenerative diseases, such as osteoarthritis (OA), Diabetes Mellitus (DM), stroke, and heart failure [104–108]. Flemming et al. conducted a review analyzing the role of EVs as biomarkers and therapeutic tools in dermatologic conditions. They considered EVs to be central in immune modulation and inflammation signaling, particularly in psoriasis and AD, and hypothesized that they may alter T-cell polarization to reduce clinical symptom scores. Similarly, they analyzed the role of EVs in the polarization of M2 macrophages, an important immune cell phenotype in wound healing. They highlighted the use of EVs in wound healing, psoriasis, and AD, and they appear to modulate a wide variety of biological functions [109]. Exosomes are nanoscale EVs that offer several size advantages: they can easily penetrate organs and skin due to their size; they do not undergo the bystander effect, retaining their properties even in an immunosuppressive environment; and they can be stored long term [56]. Research in regenerative aesthetics has focused in recent years on stem cell-derived exosomes, referring mainly to exosomes secreted by adipose stem cells (ASC-exos), mesenchymal stem cells (MSC-exos), and pluripotent stem cells [110]. MSC-exos and exosomes in body fluid have been found to participate and improve wound healing [111]. Studies conducted on murine umbilical cord-derived MSC-exos have been shown to optimize fibroblast characteristics, thus inducing wound healing in the skin [112]. Their use has been postulated also in AD, psoriasis, SLE, and cutaneous systemic sclerosis [112–115]. Exos have also been shown to improve Collagen Type I production and decrease MMPs [116] and to revert senescence-induced alterations in dermal fibroblasts [117]. Park et al. evaluated the clinical efficacy of combining ASC-exos and microneedling on 28 subjects. The results showed improvement in the GAIS and clinical improvements in skin wrinkles, elasticity, hydration, and pigmentation [118]. Tang et al. showed that ADSC-Exos promote healthy hair growth and counteracted the inhibitory effects of DHT on hair growth, using human hair follicle organs, in vitro dermal papilla cells, and in vivo animal models. They found that ADSC-Exos increased the levels of glycogen synthase kinase-3β-phosphorylated Ser9 and facilitated the nuclear translocation of β-catenin, which could be blocked by the specific inhibitor of the Wnt/β-catenin signaling pathway, the Dickkopf-binding protein [119].

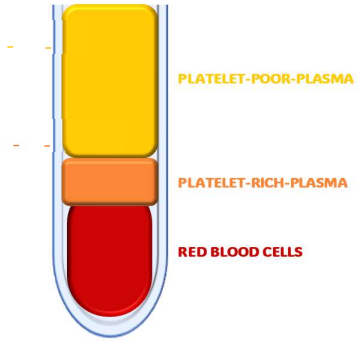

Figure 3. Platelet-rich plasma (PRP): Concentration and collection of autologous platelet-rich plasma by centrifugation.

3.3. Aesthetic Regenerative Scaffolds (ARS)—Calcium Hydroxyapatite (CaHA), Hyaluronic Acid (HA), and Poli-L-Lactic Acid (PLLA)

Since the beginning, aesthetic medicine has used biomaterials-based injectables for anti-aging and rejuvenation purposes. An inflammatory response occurs at the injection sites, causing a range of outcomes, from tissue regeneration to fibrosis. This is the basis for the concept of Aesthetic Regenerative Scaffolds (ARSs): the injection biomaterial can predetermine the inflammatory response. The ARSs are defined as biomaterials that inhibit a chronic inflammatory response, reverting fibrosis and enhancing physiological tissue regeneration. They include Calcium Hydroxyapatite (CaHA), Hyaluronic Acid (HA), and Poli-L-Lactic Acid (PLLA) dermal fillers [50,52–54]. ARSs have historically been considered as space supports and barriers, typically inert and non-bioactive, lacking regulatory properties of tissue regeneration [45]. However, several in vitro and in vivo studies have shown local modulation by the ARSs of collagenogenesis, fibrosis, and immune activity [53,54,120,121]. Courderot-Masuyer et al. conducted a study performing biopsies on the wrinkled and normal aged skin of three patients. The results showed that a mixture composed of CaHa tends to restore the contractile properties of aged fibroblasts to the same level as normal fibroblasts [121]. Gonzalez et al. evaluated 15 patients with changes in the presence of elastic fibers, proteoglycans, and elastin in photodamaged skin after injections with CaHa. An evaluation at 6 months showed that CaHa can increase proteoglycans (76%), influencing also elastin, and induces the remodeling of ECM [53]. HA has always been a major player in aesthetic medicine, as it is the most common dermal filler in use [122]. HA participates in several skin biochemical processes. First known for its face-filling characteristics, it has also been used in skin rejuvenation for years [57]. It is a non-sulfated glycosaminoglycan (GAG) that has the rheological property of holding ≈ 1000 times its weight of water [123]. At the skin level, HA associates with CD44. Interactions between CD44 and HA mediate the binding of Langerhans cells to HA in the ECM. The receptor for hyaluronan-mediated motility (RHAMM) is also expressed in human skin and mediates the TGF-β1-induced stimulation of fibroblast motility [122,124,125]. Seok et al. injected six middle-aged male subjects with 2 mL of HA filler to evaluate its efficacy in terms of transepidermal water loss (TEWL), hydration level (corneometer), patient satisfaction, and the GAIS [126]. Williams et al. injected 15 healthy subjects with microdroplet placement of hyaluronic acid in aging hands [127]. Both studies showed improvement in clinical appearance, patient satisfaction, and skin parameters [126,127]. Yutskovskaya et al. conducted a randomized, comparative, clinical study and an immunohistochemical analysis on eight adult females to assess the efficacy of the combined use of CaHa and HA fillers in terms of skin quality improvement. A comparative analysis of histological changes in skin tissue revealed that the simultaneous or consequential injection of HA and CaHa results in skin remodeling and that the combined use of HA and CaHA has a considerable impact on aging and skin remodeling due to the ECM accumulation of elastic fibers [128]. PLLA is an alpha hydroxy acid polymer of the L-Lactic Acid that has been used in regenerative medicine for more than 30 years [54,129,130]. The most known property of PLLA is volume

restoration [54,131], but its ability to induce collagen synthesis has also positioned it as a tool in regenerative medicine [132,133]. In the field of rejuvenation, PLLA has been used for years, in numerous clinical trials in different areas and indications (Table 2), not only for volume enhancement but also for contouring and wrinkle correction [131,134,135]. A study was conducted by Zhu et al. on PLLA-inducted collagen synthesis in a cultured dermal fibroblast. Increased PLLA concentrations resulted in the production of procollagen, elastin, COL1A1, COL1A2, TIMP-1, TIMP-2, and tGF-β and attenuated the expression of MMP-1. The results confirmed that PLLA promotes the collagen gene expression and synthesis by the TGF-β/Smad signaling pathway [136]. This results clinically in cross-sectional use for skin rejuvenation of the face and body, including edematous fibrosclerotic panniculopathy (EFP). Swearingen et al. enrolled 31 healthy women with EFP, administering PLLA (treatment group) or saline (control group) injections combined with subcision into each of the glutes or thighs. After 3 and 6 months, significant changes in the global aesthetic improvement scale (GAIS) and the cellulite severity scale (CSS) were reported [137]. In the field of regenerative scaffolds, it is also worth mentioning bacterial cellulose (BC), which has been studied as a biomaterial for cartilage regeneration and wound healing [138,139]. However, its use in the field of cosmetic dermatology remains unexplored.

Table 2. Relevant studies on the use of PLLA for aesthetic regenerative purposes.

Reference	Type of Study	Results
Zhu et al. [136]	In vitro (Cultured fibroblasts)	PLLA induces collagen synthesis in cultured dermal fibroblasts. PLLA promotes the collagen gene expression and synthesis by the TGF-β/Smad signaling pathway [136].
Swearingen et al. [137]	In vivo (31 healthy women)	PLLA is useful in treating edematous fibrosclerotic panniculopathy (EFP). After 3 and 6 months, it leads to significant changes in the global aesthetic improvement scale (GAIS) and the cellulite severity scale (CSS) [137].
Goldberg et al. [140]	In vivo (14 healthy subjects)	PLLA injection induces a significant increase in collagen types 1 and 3 without an appreciable accompanying inflammatory response [140].

4. Conclusions and Future Directions

Aesthetic dermatology represents a thriving field of application of regenerative medicine, gaining attention and popularity across different generations. While previously reserved for the over-50 population, it now represents a field with a large and expanding target population. The regenerative treatments analyzed in our review focus on the punctual compensation of factors (Bio-Cues) or cells (ASCs and nanofat) and on the induction of regenerative effects by injection of biomaterials (ARSs). Although the theoretical substrate is favorable for the application of regenerative techniques on an aesthetic–dermatological level, the method is not yet standardized and lacks consensus, so the evidence in the literature is variable and often unsatisfactory. Our hypothesis regarding the weaknesses of the abovementioned techniques relates to their punctual nature. The pathophysiology of skin regeneration is not a punctual process but rather a sequential one. The initiation of the skin's regenerative potential occurs as a result of a triggering cause, with the launching of a chain of events, starting with platelets and the derived activity and extending to stem cell differentiation and fibroblastic activation. In the context of regenerative dermatology, the ensemble of consequential processes should be considered as building blocks in the restoration and enhancement of skin regenerative capacity. This perspective may suggest why the theoretical substrate of the three mentioned pillars (cells and cell derivatives, Bio-Cues, and ARSs) struggles with the clinical evidence, which is, in some cases, unsatisfactory. In our vision, the use of schemes involving the activation, via physio-mimetics, and proliferation of quiescent stem cells through growth factors (e.g., VEGF, FGF, PDGF-B, and TGF-β), with the subsequent stabilization of results over time with components of the ECM (e.g., amino acids, collagen, and choline), could represent a therapeutic strategy that mimics the

pathophysiology of skin regeneration. The clinical application of regenerative medicine methods in dermo-aesthetics cannot exclude the physiological mechanisms of stem cell action, so the treatment scheme cannot be monotherapeutic and punctual but multi-target and sequential, including steps of activation, stimulation/enhancement, and maintenance. We believe that understanding the pathophysiology of skin regeneration has paved new paths toward a new era of cosmetic dermatology, comprising therapeutic schemes that mimic physiological pathways.

Author Contributions: Conceptualization, H.I.G., G.P., F.T. and S.C.; validation, H.I.G., G.P., F.T. and S.C.; formal analysis, H.I.G., S.G., G.V., L.C. and S.M.; investigation, F.T.; resources, F.T. and S.M.; data curation, F.T.; writing—original draft preparation, F.T.; writing—review and editing, F.T., S.P.N. and S.M.; visualization, F.T.; supervision, S.G., S.C., H.I.G., S.P.N. and G.P.; project administration, G.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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