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Research Progress of Poly-L-Lactic Acid Microspheres for Facial Rejuvenation: Degradation Behaviors, Collagen-Inducing Mechanisms and Composite Modification Strategies

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Abstract. Current dermal fillers for aesthetic applications commonly suffer from the trade-off between therapeutic efficacy and durability. Hyaluronic acid (HA) merely delivers short-term soft-tissue augmentation, whereas autologous collagen transplantation is limited by donor-site availability. It has been demonstrated that poly-L-lactic acid microparticles (PLLA) de novo induce the formation of autologous collagen. However, the continuous release of lactic acid, which accompanies the hydrolytic degradation of the material, can lead to erythema and subcutaneous nodules, and the collagen-stimulating potential of PLLA still awaits further improvement. Based on new evidence from domestic and international sources, this review outlines the cellular and molecular changes underlying skin aging, contrasts the behavior of the three polylactic acid stereoisomers—PLLA, PDLA, and PDLLA—and clarifies the mechanistic cascade through which PLLA microparticles drive collagen biosynthesis. The synergistic effects of combining PLLA with hyaluronic acid, bioactive glass, tranexamic acid (TXA), and native collagen are also systematically evaluated. Key challenges in microsphere production and multi-component mixing are highlighted, while substrate modification and multifunctional composite systems are proposed as promising directions for future research, thus serving as a reference point for the development of next-generation regenerative aesthetic fillers.

Keywords: Poly-L-lactic acid, facial rejuvenation, collagen regeneration, composite modification

1. Introduction

1.1. Mechanisms of facial aging

The alternating endogenous factors and photoaging work together to disrupt the homeostasis of dermal collagen and modify the biological activity of fibroblasts, thereby leading to the disruption of collagen metabolism. This molecular pathological phenomenon results in the appearance of facial wrinkles and a reduction in tissue volume. Ao et al. [1] established an in vitro model of oxidative effects in human dermal fibroblasts induced by UVB radiation. CCK-8 analysis, Transwell

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migration test, and qPCR were conducted on the control group and the UV irradiation group to characterize cell proliferation and migration phenotypes as well as the expression levels of collagen-related genes. The reactive oxygen compounds produced by UV irradiation inhibit TGF-β secretion, impede fibroblast proliferation and migration, regulate the expression of collagen-degrading genes MMP1 and MMP3, and accelerate the degradation of type I and type III collagen fibers. These results reveal the cellular mechanism by which light alternation affects the integrity of skin structure. Xu et al. [2] conducted a large-scale systematic validation, including 42 sets of human skin biopsy data sets, which were from subjects of different ages and exposed to varying degrees of sunlight. Parameters such as dermal collagen density, fibroblast density, and TGFβ/SMAD signaling activity were evaluated.

1.2. Industrial landscape of PLLA microspheres

PLLA droplets are the main component of commercially available biostimulating injectables of poly-L-lactic acid [3-5]. Among the stereoscopic polymer family, the PDLA and PDLLA isomers exhibit significantly different degradation curves. Comparative evidence indicates that PDLA, due to its high in vivo crystallinity, can last for more than 30 months, prolonging the action time, resulting in subcutaneous retention and gradual hardening. Table 1 shows the degradation performance of three different poly-lactic acid configurations. In contrast, the completely amorphous PDLLA undergoes rapid hydrolytic degradation within approximately 6 months, which prevents any persistent collagen stimulation. Between these two extremes, PLLA exhibits medium crystallinity and uniformly degrades within 12 to 24 months, the time sequence being closely related to the clinical process of cosmetic regeneration [6-10]. Overall, Sculptra (Godema) is recognized as the first injectable agent based on PLLA to receive regulatory approval. It was initially authorized in the European Union for correcting fat malnutrition in 1999 and later extended to the management of facial pockets. A large number of preclinical and clinical studies have been accumulated around this commercial product. Although early studies mainly focused on the elimination kinetics of pure PLLA microspheres, recent attention has turned to combined binary formulations. Aesthefill is a porous poly-caprolactone excipient synthesized in South Korea, aiming to achieve more satisfactory immediate volumeization. Foreign research usually benefits from a more mature preclinical platform and long-term follow-up clinical data. In contrast, national research and industrialization started later but developed rapidly in the last century. Companies such as Changchun Siboma and Suzhou Nanowe Life in China have established scalable production of PLLA medical droplets, and domestic authorized products - especially Rubaitian (Aimeike) and Aiweilan (Siboma) - rely largely on the PLLA-HA composite material strategy. Chinese academic work focuses on reducing the two inherent limitations of pure PLLA: the release of acid degradation products and the low cell-matrix interaction. However, there are still challenges, including the consistency of loading in a single manufacture, the lack of large samples, and long-term clinical evidence. Most existing publications deal with the constituent materials separately, except for composite systems based on HA, bioactive glass, or natural collagen protein, lacking face-to-face comparisons. Through the analysis of international literature, this study aims to compare different composite material strategies to formulate guidelines for continuous improvement of regenerative fillers. Aging mechanisms and products are shown in Figure 1.

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Table 1. Degradation-related properties of PLLA, PDLA and PDLLA

Material type	Degradation cycle	Mechanical property
PLLA	12-24 months, homogeneous degradation	Moderate, good support
PDLA	Over 30 months, slow degradation	High rigidity (high crystallinity)
PDLLA	Under 6 months, rapid hydrolysis	Low strength (amorphous structure)

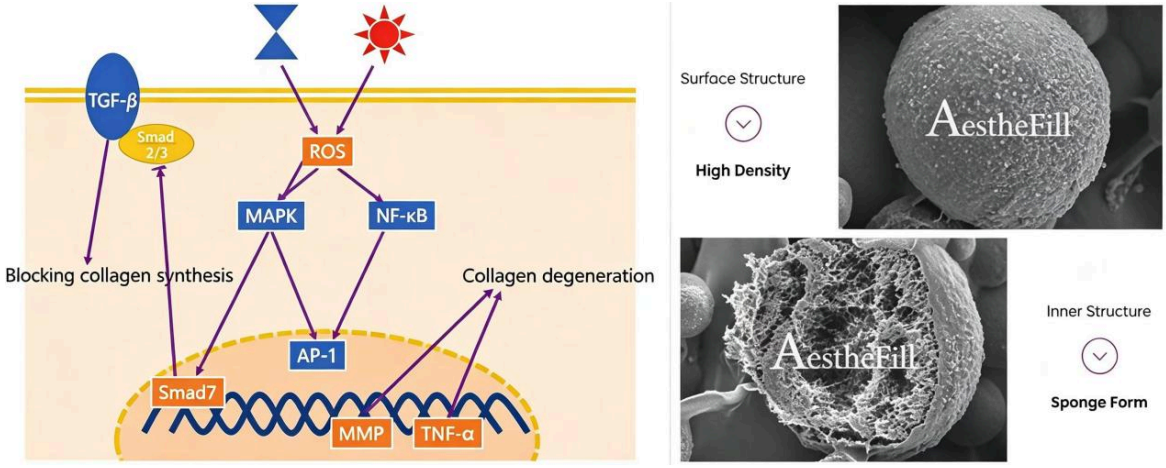


Figure 1. Schematic illustration of facial aging mechanism and product micrographs

2. Mechanisms underlying plla-mediated facial rejuvenation

2.1. Hydrolytic degradation and foreign-body response

During the subcutaneous implantation process, PLLA undergoes hydrolytic degradation and releases lactic acid, causing a mild inflammatory response to the foreign body - usually well tolerated - which subsequently activates collagen synthesis through the TGF-β/SMAD signaling pathway. However, the continuous accumulation of lactic acid leads to local acidification, which may cause adverse effects such as erythema or the formation of granulomas. In the rat implantation model evaluated for tissue response using immunohistochemistry and immunofluorescence, Geara [7] demonstrated that the lactic acid released by PLLA hydrolysis promotes the polarization of macrophages to the M2 repair phenotype, activates the TGF-β/SMAD signaling chain, increases the transcription of genes involved in collagen production, and improves the production of type I and type III collagen by fibroblasts. Additionally, lactic acid helps with cellular energy metabolism by integrating into the tricarboxylic acid cycle. Li [8] conducted a five-year follow-up on 127 subjects who received ultrasound-PLLA injections. Within 12 to 24 months, the material gradually degraded, while the volume effect supported by the newly formed collagen persisted for 2 to 3 years. However, approximately 21% of the participants developed erythema or granulomas, confirming that acidification caused by lactic acid accumulation is the main cause of these side effects [11, 12].

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2.2. Microenvironmental modulation of degradation and active-agent release

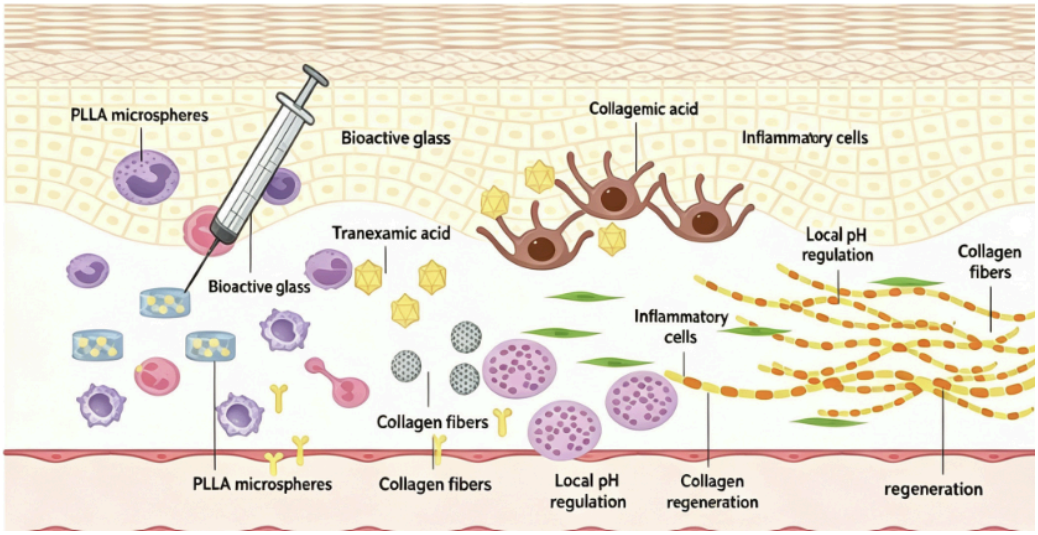


Figure 2. Schematic diagram illustrating fibroblasttriggered collagen secretion and invivo degradation behavior

The Sauere microstructure accelerates the random separation of ester bonds in the PLLA chain, accelerating material degradation and reducing the collagen stimulation window. Bioactive glass creates a weakly alkaline environment, delaying the hydrolysis of PLLA and prolonging the regenerative effect, reducing the inflammatory cascade. Tranexamic acid (TXA) inhibits excessive immune activation at the signal level. The combined application maintains the efficacy of collagen induction and alleviates the erythema and stinging after injection. Zhao et al. [13] designed two experimental groups (pure PLLA microdroplets and glass/PLLA bioactive composite microdroplets) for in vitro degradation tests and subcutaneous implants in nude mice. In vitro monitoring of pH changes and mass loss [14]. In animal studies, the tissue pH, inflammatory cell phenotype, and collagen accumulation were quantified at predetermined times. Bioactive glass releases Ca^{2+} and Si^{4+} during hydration, neutralizing hydrolyzed lactic acid and maintaining a physiological pH close to the implant site. This process slows down the dissociation of esterification in PLLA, prolongs the regenerative time, and reduces neutrophil infiltration and local inflammation. Kim et al. prepared injectable TXA-loaded dextran hydrogel and evaluated its bioefficacy using an LPS-stimulated inflammatory model and subcutaneous implants in mice. The sustained release of TXA regulates pro-inflammatory mediators, including TNF-α and IL-6, inhibits the fibrinolytic pathway, reduces postoperative bleeding and bruising, and does not interfere with fibroblast proliferation or collagen synthesis. Cui et al. [15] developed porous PLA grids rich in TXA to characterize the drug release profile. The in vivo results showed that TXA regulates macrophage polarization, inhibits abnormal responses to external attacks, and reduces the risk of granuloma outside the implant. These results confirmed the feasibility of integrating TXA into PLLA microspheres to increase skin viability. Figure 2 shows the graph of collagen secretion triggered by fibroblasts and in vivo hydrolysis behavior.

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3. Composite-modified PLLA microspheres

3.1. PLLA-hyaluronic acid composites

Neat PLLA microspheres are limited by the absence of immediate volumizing effects post-injection. Composite strategies incorporating hyaluronic acid, bioactive glass, TXA or native collagen can respectively resolve deficiencies in instant filling, acid-mediated irritation, pathological inflammation and cell-material compatibility, catering to diverse anti-aging demands across distinct facial anatomical regions. The PLLA-HA hybrid combines the direct volume and hydration properties of HA with the long-term bioactive collagen-enhancing activity of PLLA. The reduction in PLLA load alleviates inflammation associated with lactic acid, making this mixture particularly suitable for sensitive surface areas such as tear-stained areas and nasolabial folds. Su et al. [16] conducted a prospective controlled clinical study involving 62 patients with nasolabial wrinkle reduction and tear days. The participants were randomly divided into pure PLLA or PLLA-HA groups, with standardized injection dose and depth. Immediately after treatment and at 1, 3, 6, and 12 months of follow-up, standard parameters such as Faltenschwerg score, skin thickness, and incidence of adverse reactions were recorded. The soft tissue of the PLLA-HA group increased immediately, which was attributed to HA [17]. HA gradually metabolizes within approximately six months, while PLLA continues to promote endogenous collagen secretion. At 12 months, skin thickness showed sustained clinical improvement. Compared with the pure PLLA cohort, a single reduction in PLLA dose resulted in significantly lower incidences of stinging and erythema. Oh [18] conducted a systematic analysis of 11 preclinical and clinical studies on PLLA-HA load, integrating immunohistochemical data of collagen and indications of human safety and efficacy. The combined PLLA-HA compound maintains the biostimulatory ability of PLLA, while the HA matrix uniformly disperses microspheres to avoid local lactate accumulation induced by particle aggregation. This reduces acute inflammation after injection and balances temporary contour correction and long-lasting collagen regeneration.

3.2. PLLA-bioactive glass composites

Bioactive glass (BG) is an inorganic biomaterial focused on regeneration, with its main components being SiO2, CaO, and P2O5. It is highly praised for its adjustable ionic behavior, good tissue integration, and low cytotoxicity. Initially developed for bone repair, its indications later expanded to support skin and soft tissue regeneration [19-26]. Zhao et al. prepared PLLA composite microspheres containing BG with multiple doping levels by evaporating the solvent, and then evaluated them through in vitro degradation tests, cytological analysis, and subcutaneous implantation in nude mice. Continuous measurement was made of pH changes related to degradation. Human dermal fibroblasts were used to study the cell fixation, proliferation, and expression of collagen genes, while in vivo tissue analysis was used to assess local pH, inflammatory infiltration, and secretion of type I and type III collagen. The ionic products released by BG buffer the pH of the implant, thereby alleviating the stimulation of lactic acid. A bioactive layer similar to hydroxyapatite also grew on the composite microscope surface, significantly promoting the adhesion and diffusion of fibroblasts. Then, the histological part showed that compared with the pure PLLA group, the deposition of type I and type III collagen was significantly higher in the combined group. Dong et al. [27] established a murine subcutaneous implantation model with neat-PLLA and PLLA/BG groups. Flow cytometry and immunofluorescence were adopted to characterize macrophage polarization and inflammation-regeneration-related mediators.

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Ions leached from bioactive glass promoted M2-type macrophage polarization, suppressed pro-inflammatory mediator secretion, optimized biomaterial-tissue interfaces, facilitated homogeneous microsphere degradation in vivo, and decreased the incidence of long-term complications such as induration and granuloma [28-31].

3.3. PLLA-tranexamic acid composites

TXA-loaded PLLA microspheres exploit the hemostatic and anti-inflammatory pharmacological actions of tranexamic acid to limit injection-associated hemorrhage and ecchymosis and to restrain excessive macrophage infiltration. Crucially, this is achieved without sacrificing the collagen-inducing bioactivity of PLLA; rather, TXA blocks the pathological amplification of the foreign-body inflammation evoked by PLLA, a property that proves especially valuable in highly vascularized territories such as the periorbital zone and the mid-face. Zhao et al. prepared injectable porous PLLA–HA–collagen hydrogels loaded with TXA, employing TXA-free counterparts as controls. To determine the in vitro release kinetics of TXA, high-performance liquid chromatography (HPLC) was used. In the animal stage, subcutaneously implanted SD mice were used to quantify the levels of TNF-α and IL-6 in the tissues, and histological examination was used to evaluate bleeding and bruising. The composite hydrogel allowed for the continuous and prolonged release of TXA, inhibited local fibrinolytic activation, reduced treatment bleeding and bruising, while weakening inflammatory signals without interfering with fibroblast-induced collagen synthesis. As further demonstrated by Kim et al., an appropriate dose of TXA did not weaken the biological stimulation induced by the biomaterials, but effectively alleviated the acute inflammation after injection, thereby providing significant safety benefits for the vascular-rich orbital region.

3.4. PLLA-collagen composites

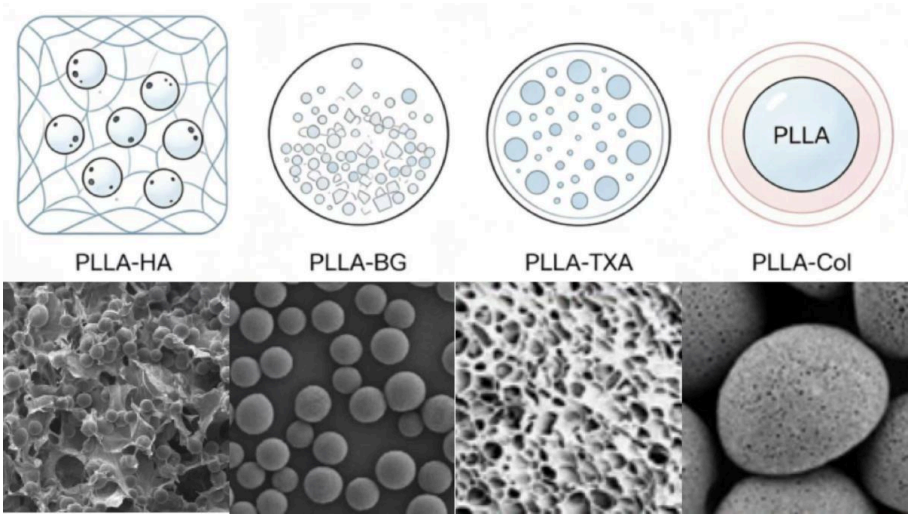


Figure 3. Compositemodified PLLA microspheres

Natural collagen has compositional homology with the extracellular matrix of human dermis. When incorporated into the PLLA-based formulation, it provides immediate volume filling, improves the interaction between microspheres and cells at the interface, and mitigates the response to foreign substances - these properties make this combination particularly suitable for delicate and sensitive skin areas such as around the eyes and the neck. Zhao et al. dispersed porous PLLA

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microspheres within HA-native-collagen hydrogel matrices to produce injectable composites; neat PLLA suspension was used as control. Rheological characterization evaluated injectability. Fibroblast adhesion behavior was observed in vitro. Nude-mouse subcutaneous implantation assessed immediate volume retention, histocompatibility and collagen deposition. Collagen-containing hydrogels exhibited favorable plasticity and instant defect filling upon injection. Fibroblasts displayed superior attachment and spreading on composite matrices, and early foreign-body inflammatory reactions were milder in vivo. Park et al. surface-functionalized PLLA microspheres with type-I native collagen via physical coating. The properties of different composite modified PLLA microspheres are shown in Table 2. Surface topography was characterized, followed by in-vitro cellular assays and subcutaneous injection in a sensitive-skin mouse model. Collagen coating improved microsphere hydrophilicity and markedly enhanced fibroblast adhesion and proliferation. In-vivo observations demonstrated dampened inflammatory responses and reduced cutaneous erythema for collagen-coated PLLA microspheres, indicating suitability for thin sensitive-skin augmentation [32]. As shown in Figure 3, different composite modified PLLA microspheres are presented.

Table 2. Properties of composite-modified PLLA microspheres

Composite formulation	Component configuration	Fabrication strategy	Degradation and release profile
PLLA-HA	PLLA microspheres dispersed within HA hydrogel matrix	Physical suspension blending	Integrated system with ~6-month HA metabolism coupled to 12-24-month homogeneous PLLA degradation
PLLA-BG	PLLA matrix incorporated with bioactive-glass particulates	Emulsification-solvent-evaporation method	BG-ion-mediated acid buffering retards the hydrolytic degradation of the PLLA matrix
PLLA-TXA	Porous PLLA microspheres loaded with tranexamic acid	Porous-adsorption impregnation	8-week sustained TXA release synchronizes with steady PLLA degradation free of burst effect
PLLA-Collagen	Collagen-coated PLLA microspheres or PLLA dispersed in HA-collagen hydrogel	Physical coating / physical blending	Collagen rapid turnover; PLLA enables long-term regeneration

4. Challenges and future perspectives

4.1. Obstacles in material fabrication and structural controllability

Current PLLA-microsphere manufacturing and multi-component blending techniques suffer from insufficient reproducibility. Hydrolysis-derived acid production represents an intrinsic material limitation that can only be alleviated rather than fully eliminated by excipients. Formulations customized according to variable facial-skin-thickness profiles remain absent. Conventional emulsification techniques cannot precisely regulate microsphere dimension and pore geometry. Heterogeneous particle-size distribution results in asynchronous subcutaneous degradation and spatially uneven inflammatory distribution. Weak interfacial adhesion between dissimilar phases in

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multicomponent systems causes premature leakage of embedded bioactive moieties and substantial batch-to-batch performance fluctuation. Given PLLA's molecular structure, lactic-acid generation during hydrolysis is unavoidable; existing composite adjuvants only partially counteract acid-associated irritation. Distinct anatomical sites (periorbital area, cheek, neck) exhibit divergent skin thickness and metabolic rates, yet site-specific formulations with tailored particle-size and degradation kinetics have not been established.

4.2. Development of multifunctional modification systems

In the future, two important directions for future work can be determined. The first involves molecular engineering of the PLLA network to inhibit the production of lactic acid; the second focuses on designing an integrated ternary composite system capable of performing load-bearing, acid buffering and antioxidant functions. Similarly, efforts should be directed towards microspheres in specific regions and standardized manufacturing processes. Copolymerization constitutes a feasible strategy for the reorganized PLLA segments, thereby reducing the total release of lactic acid during degradation. At the same time, the simultaneous integration of hyaluronic acid, bioactive glass and anti-inflammatory agents enables the manufacture of single-chip microspheres, combining immediate volumeization, long-term stimulation of collagen and anti-reaction properties in a single component. Microfluidics allows for the manufacture of uniformly sized monodisperse microbeads. The microsphere characteristics that adapt to different facial regions can simplify clinical procedures, improve patient safety and satisfaction.

5. Conclusions

5.1. Development of multifunctional modification systems

Unlike traditional physical additives, PLLA plays an anti-aging role by stimulating endogenous collagen repair. Through combined modification with various functional adjuvants, PLLA overcomes limitations such as insufficient immediate contour correction, acid stimulation, and suboptimal cell compatibility, thereby covering a wide range of anti-aging clinical fields and having the prospects of transformation and commercial research. Traditional hyaluronic acid or calcium-based additives only provide temporary mechanical support, while PLLA induces the intrinsic new formation of collagen, fundamentally improving atrophy and wrinkles. The combined formula is combined with hyaluronic acid salts, bioactive glass, or natural collagen to alleviate the shortcomings of pure PLLA and provide customized solutions for thin surface lines, deep volume loss, and thin sensitive skin. Multidisciplinary clinical data show that the patient satisfaction of the composite PLLA additive is as high as 94%, reflecting stable clinical performance and strong commercial potential.

5.2. Outlook for substrate modification and multifunctional composite systems

The modern PLLA composite material system is still limited by the restricted manufacturing precision and the insufficient stability when mixing multiple components. Therefore, it is expected that future research will make progress on two main axes: the molecular technology of the PLLA substrate, aiming to optimize its degradation and reduce the stimulation induced by lactic acid, as well as the creation of multifunctional integrated biomaterials with hygroscopic, anti-inflammatory and collagen-friendly properties. At the same time, the existing composite microbeads are still

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fragile in terms of manufacturing rigidity and can only be used under strict limitations. To overcome these obstacles, the next step should be to integrate the PLLA polymer scheme to alleviate the stimulation caused by the release of hydrolytic acids and integrate multiple functional additives, enabling a single biomaterial to cover different anatomical sites. With the continuous improvement of microsphere polymerization and manufacturing technologies, the PLLA composite microspheres, with low irritation and high collagen induction efficiency, will become the preferred choice for the next generation of anti-aging skin regeneration substitutes.

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