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Modulatory pathways of PLLA-SCA™: New insights for aesthetic regenerative science

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Historical perspective

Poly-L-lactic acid – PLLA-SCA™ (Sculptra®, Galderma) has been certified in Europe since 1999, with approval for marketing in the USA since 2004, and for aesthetic use in the USA since 2009. In 2023, the USA Food and Drug Administration also approved it for the treatment of cheek wrinkles.[1] More recently, the EU certified the expansion of PLLA-SCA™ indications to include body areas such as the décolletage, gluteal region, posterior thighs, and upper arms.[2]

Subsequent clinical trials have progressively elucidated the properties and therapeutic potential of PLLA-SCA™, revealing a broad spectrum of mechanisms of action and clinical benefits, including facial rejuvenation, improvement in skin laxity and quality, volumetric restoration in areas of tissue depression, and sustained stimulation of collagen production. Over the past two decades, extensive global experience has consolidated the safety and effectiveness of this biostimulatory implant.[2–7] This broader therapeutic understanding has suggested the vast potentiality of use of PLLA-SCA™ beyond the facial region, including the neck, décolleté, arms, abdomen, thighs, and buttocks, and more recently in body contouring, with notable aesthetic benefits in addressing gluteal volume deficiency, tissue flaccidity, and cellulite. The adoption of refined injection techniques and patient-specific treatment planning has contributed to increasingly predictable and reproducible clinical outcomes.[2,7–11]

Mechanisms of action

Neocollagenesis

PLLA-SCA™ is a biocompatible and biodegradable implant that stimulates endogenous collagen production through controlled inflammatory processes. While PLLA-SCA™ particles degrade over approximately 18 months, their clinical effects may persist for up to 25 months, offering natural and durable improvements in skin structure and volume.[6,12,13] Following deep dermal or subcutaneous injection administration, PLLA-SCA™ microparticles initiate a localized biological response characterized by microparticle encapsulation, fibroblast recruitment, and subsequent collagen synthesis. This cascade ultimately leads to progressive dermal remodeling and skin firming. The product's effectiveness relies on the host's capacity to generate a regulated inflammatory reaction, triggering a cascade involving monocytes, macrophages, and fibroblasts, which collectively support tissue regeneration and long-term clinical efficacy.[2,14–16] Notably, *in vivo* studies have demonstrated that PLLA-SCA™ induces a 66.5% increase in type I collagen synthesis after just three months of treatment, underscoring its robust neocollagenesis potential.[17] Additionally, dermal thickness has been shown to improve by 73% at 12 months, contributing to significant skin reinforcement and structural remodeling over time.[18]

As our understanding of PLLA-SCA™ has evolved beyond its collagen synthesis capability, emerging data provide additional insights into its regenerative effects within a controlled and localized biological response. These mechanisms encompass three key biological domains beyond the classical stimulation of type I and III collagen synthesis, which are central to dermal structural support: (i) elastogenesis, supporting the recovery of the skin's biomechanical elasticity; (ii) modulation of the local immune microenvironment, favoring a regenerative profile; and (iii) effects on adipose tissue, contributing to the restoration of subcutaneous volume. The following sections elaborate on these mechanisms, highlighting how PLLA-SCA™ engages complex signaling pathways to promote integrated dermal and adipose tissue regeneration.[1,2,16,19,20]

Elastin Synthesis

Emerging evidence suggests that PLLA-SCA™ contributes to elastin synthesis through unique cellular and molecular pathways which are presented in a 3D human skin model incorporating macrophages. Huth et al.,[19] demonstrated that PLLA-SCA™ enhances fibroblast activation via macrophage-fibroblast crosstalk. PLLA-SCA™ treatment upregulated genes such as LAMA3 and ITGA6, which are essential for dermal-epidermal junction integrity and establish a microenvironment conducive to ECM production, including elastin. Furthermore, increased expression of cytokines and chemokines, notably TGFB2, CXCL6, and IL1B, were observed, implicating these molecules in the stimulation of collagen I synthesis and elastin deposition. Clinically, this mechanism correlates with a 34% improvement in elastin quality observed as early as 3 and 6 months, thereby enhancing skin elasticity and structural resilience in treated areas.[21]

Effects on adipose tissue and local tissue environment

Beyond its established role in neocollagenesis and extracellular matrix remodeling, PLLA-SCA™ has been associated with broader regenerative effects, particularly in relation to adipose tissue and local biological responses. Gene expression analyses have suggested that PLLA-SCA™ may induce a distinct transcriptional profile in

human dermal cells, with upregulation of genes involved in collagen biosynthesis (e.g., COL1A1, COL3A1, COL5A1) and extracellular matrix turnover (e.g., MMPs, TIMPs), as well as pathways related to wound healing (e.g., ACTA2, DKK1, HGF), immune modulation (e.g., IL-4, IL-13, IL-10), and adipocyte-related processes (e.g., ADIPOQ, PLIN1, LEP, and FABP4).[2,22,23]

Notably, the mechanism of action of PLLA-SCA™ also appears to involve M2 macrophage polarization, a reparative immune phenotype, and subsequent ECM modification, which together initiate localized tissue remodeling with upregulation of transforming growth factor beta (TGF-β). PLLA-SCA™ stimulates a regenerative signaling cascade characterized by the upregulation of adipokines, bioactive mediators secreted by adipocytes that enhance dermal structure, metabolic homeostasis, and tissue repair.[16,20,23,24] These findings reinforce a broad biostimulatory capacity of PLLA-SCA™ to coordinate both dermal and adipose regeneration through synergistic interactions between fibroblasts, adipocytes, and M2-polarized macrophages (Figure 1 & 2).

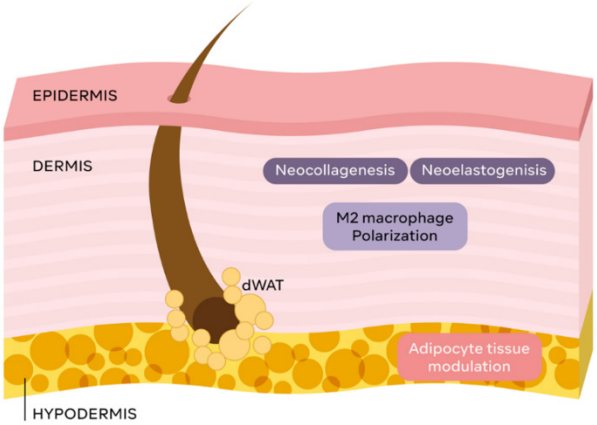

Figure 1 PLLA-SCA's pathways signaling synergistic interactions between fibroblasts, adipocytes, and M2-polarized macrophages.

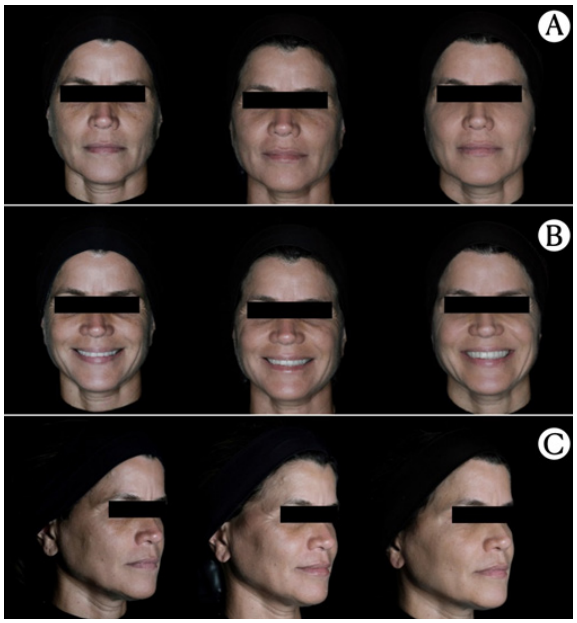

Figure 2 Female patient treated with PLLA-SCA (three sessions, one vial per session at monthly intervals) and hyaluronic acid (OBT™ for the perioral region [HA_{DEF}], and lips – [HA_{KYS}]). Images at pre-treatment and at 3 and 6 months post-treatment. (A) Frontal at rest; (B) smiling; (C) oblique views. Restoration of volume and progressive improvement in skin quality (images courtesy of the authors).

Collectively, these mechanisms enable PLLA-SCA™ to influence all three structural layers of the skin, including the epidermis, dermis, and hypodermis, promoting coordinated tissue regeneration that restores dermal integrity, improves biomechanical resilience, and contributes to a more rejuvenated cutaneous appearance.[16,20,23,24]

Future directions and conclusion

Over the past 25 years, PLLA-SCA™ has evolved from a facial filler to a multifunctional regenerative agent capable of modulating critical biological processes such as neocollagenesis, neoelastogenesis, M2 macrophage polarization, and adipose tissue modulation. As scientific understanding of its cellular mechanisms continues to advance, particularly in terms of fibroblast, macrophage, and adipocyte interactions, its clinical potential is expanding through diverse and synergistic pathways in regenerative medicine. Ongoing research will be essential to further explore its mechanisms and amplify its clinical indications, particularly in extra-facial areas, reinforcing PLLA-SCA™'s position as a cornerstone in injectable aesthetic regenerative medicine.

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Conflict of interest

Dr. Haddad is speaker and investigator for Galderma. Drs. Nogueira is medical director at Galderma Brazil. Drs Leão and Gomes are medical managers at Galderma Brazil.

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