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Review Article

The Inflammaging Paradox in Aesthetic Surgery: How Systemic Senescence Blunts the Efficacy of Energy-Based Devices and Tissue Repair

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Abstract

Background: "Inflammaging", a chronic, low-grade, sterile, systemic inflammatory state that intensifies with chronological age, is increasingly recognized as a unifying driver of tissue-level aging across organ systems, yet its implications for aesthetic and reconstructive surgical outcomes have not been systematically mapped. Cellular senescence, Senescence-Associated Secretory Phenotype (SASP) activity and a progressive shift toward matrix-degrading proteolysis are each individually documented in the dermatology and gerontology literatures, but the aesthetic surgery literature has not yet synthesized how these processes converge to alter the host tissue bed that surgeons depend upon for successful outcomes.

Objective: To map the existing literature on inflammaging as it pertains to (1) the pathophysiology of facial soft-tissue aging, (2) wound healing and scar formation, (3) the efficacy and complication profile of controlled-injury aesthetic modalities (ablative/fractional resurfacing, radiofrequency microneedling, chemical peels) and (4) emerging strategies for "aesthetic prehabilitation" and to identify the research gaps that must be closed before host-tissue optimization can be adopted as a standard adjunct to aesthetic surgical planning.

Methods: A scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) framework. Twelve structured search strings across five thematic concept clusters were run in PubMed/MEDLINE on July 25, 2026, yielding 12,138 database records; 11 additional records were identified through citation chasing. Given the scale of some search yields, a relevance-ranked screening protocol (typically the top 40-50 records per search string) was applied and is disclosed transparently as a resource-constrained rapid-review adaptation rather than exhaustive screening of all raw hits. In total, 433 records were screened, 333 were excluded and 111 records were assessed at the eligibility stage, of which 110 were included in the final synthesis.

Discussion/Conclusion: The reviewed evidence supports a coherent model in which senescent dermal fibroblasts, keratinocytes and adipocytes secrete a chronic SASP that shifts the Matrix Metalloproteinase (MMP)/Tissue Inhibitor of Metalloproteinase (TIMP) balance toward net proteolysis, destabilizes the Superficial Musculoaponeurotic System (SMAS) and facial fat compartments, stalls the macrophage M1-to-M2 transition central to wound repair and predisposes to pathologic cicatrization via sustained Transforming Growth Factor-Beta 1 (TGF-β1) signaling. Because controlled-injury aesthetic modalities depend on an intact, temporally coordinated healing response, this inflammaging phenotype plausibly explains the disproportionate erythema, textural change and unpredictable neocollagenesis observed in aged and photodamaged skin-though the device-outcomes literature rarely stratifies by chronological age or senescent burden, a limitation this review makes explicit. "Aesthetic prehabilitation", combining topical senotherapeutics/regenerative biomaterials, systemic metabolic optimization and staged procedural timing, is conceptually well supported by adjacent oncologic and cardiac prehabilitation evidence but remains almost entirely untested as a named, protocolized intervention in aesthetic surgery. Validated point-of-care biomarkers of inflammaging

are similarly absent from the aesthetic-surgery literature. These converging gaps define a clear translational research agenda: standardized aesthetic prehabilitation protocols, age- and senescence-stratified device-outcome trials and biomarker-driven patient selection represent the next frontier for optimizing the host tissue bed rather than treating it as biologically inert.

Keywords: Inflammaging; Cellular Senescence; SASP; Aesthetic Surgery; Wound Healing; Prehabilitation; Energy-Based Devices; Scoping Review

Introduction

Aesthetic and reconstructive surgeons have historically approached the aging face as a problem of anatomic descent and volume loss - a mechanical deficit corrected by repositioning, resection or replacement of tissue. This framework has produced enormous technical sophistication in facelift, fat grafting and energy-based rejuvenation techniques, yet it implicitly treats the host tissue bed as a passive, biologically static substrate awaiting mechanical or thermal correction. A growing body of gerontology and dermatology literature challenges this assumption. Aging skin, subcutaneous fat and fascia are not inert; they are the visible output of an active, cell-autonomous inflammatory process termed "inflammaging", a chronic, low-grade, sterile, systemic inflammatory state, first formally articulated at the turn of the century, that is now recognized as a central driver of tissue dysfunction across virtually every organ system, including the integument [1].

Inflammaging is mechanistically distinct from, yet closely intertwined with, immunosenescence - the progressive remodeling and functional decline of the innate and adaptive immune systems with age. Immunosenescence represents an adaptive, if imperfect, response of immune networks to a lifetime of antigenic and stress exposure; inflammaging is best conceptualized as its downstream consequence, characterized by chronically elevated circulating pro-inflammatory mediators (IL-6, TNF-α, IL-1β) that are incompletely offset by anti-inflammatory counter-mediators (IL-10, IL-1Ra) [2,3]. This same aging immune landscape is paradoxically marked by a clinically documented increase in immunosuppressive activity, including expansion of regulatory T-cell and myeloid-derived suppressor-cell compartments, that coexists with, rather than resolves, the chronic pro-inflammatory tone of inflammaging, a dual phenotype with direct implications for both infection risk and impaired surveillance of dysplastic or senescent cells in aged tissue [4]. Early foundational work identified the innate immune system, particularly tissue-resident macrophages and the complement cascade, as key effectors sustaining this low-grade inflammatory tone, establishing inflammaging as a bona fide driver of age-related pathology rather than an epiphenomenon of aging itself [5].

The clinical problem this creates for the aesthetic surgeon is twofold. First, the same senescent-cell burden and SASP activity that produce the visible phenotypes of facial aging (collagen and elastin loss, SMAS and ligamentous attenuation, compartmentalized fat volume loss) also alter the tissue's capacity to heal after any surgical or energy-based intervention performed to correct those phenotypes. Second and more provocatively, several of the field's most widely used "rejuvenation" modalities are predicated on inflicting a controlled, deliberate injury to trigger a wound-healing cascade as ablative and fractional laser resurfacing, radiofrequency microneedling and chemical peels all depend on the host mounting a coordinated inflammatory-proliferative-remodeling response to convert thermal or chemical injury into durable neocollagenesis. If the aging or inflammaging host cannot reliably mount that response, the same controlled-injury paradigm that reliably rejuvenates younger, biologically robust skin may instead produce prolonged erythema, unpredictable textural change or pathologic scarring in the very patients who are the primary demographic seeking these treatments.

No existing review has systematically mapped this intersection between systemic inflammaging biology and aesthetic surgical practice. The objective of this scoping review is therefore threefold: (1) to synthesize the pathophysiologic literature connecting cellular senescence, SASP activity and MMP/TIMP dysregulation to the structural aging of the dermis, SMAS and facial fat compartments; (2) to characterize how this same biology alters wound healing, macrophage function and scar formation in ways directly relevant to incisional and post-procedural healing; and (3) to evaluate the evidence and, where evidence is absent, to explicitly identify the gap for "aesthetic prehabilitation" strategies that might optimize the host tissue bed before an elective aesthetic intervention, shifting the surgical paradigm from treating the anatomic defect alone to optimizing the biological substrate in which that defect is corrected. A scoping review methodology was selected specifically because the boundaries of this literature are fragmented across gerontology, dermatology, wound healing science and plastic surgery journals that rarely cite one another, making a structured map of the field, rather than a narrow, hypothesis-testing systematic review, the appropriate first step.

Methodology

This scoping review was conducted and is reported in accordance with the PRISMA extension for Scoping Reviews (PRISMA-ScR) checklist [1]. No prior protocol was registered; as a literature-mapping (rather than intervention-effect) scoping review with no patient-level outcome data, this is consistent with common PRISMA-ScR practice for exploratory evidence maps.

Eligibility criteria. Sources of evidence were eligible if they addressed, in humans or in mechanistically translatable animal/in vitro models, any of the following: cellular senescence or the SASP in skin, fat or fascia; MMP/TIMP balance in dermal or connective tissue aging; SMAS or facial fat compartment anatomy and age-related change; macrophage polarization, angiogenesis or epithelialization in wound repair; pathologic scar formation (hypertrophic scar, keloid, post-inflammatory hyperpigmentation); outcomes or complications of ablative/fractional CO_2 resurfacing, radiofrequency microneedling or chemical peels, particularly as modulated by age or photoaging; or prehabilitation, senolytic, regenerative-biomaterial, peptide or biomarker literature relevant to preoperative host optimization. No date restriction was applied; English-language records with an available abstract were prioritized, with a small number of foreign-language records excluded at screening where noted.

Information sources and search strategy. PubMed/MEDLINE was searched as the primary database on July 25, 2026. Embase was not accessible due to the absence of an institutional subscription at the time of the search, a limitation discussed below. Twelve structured search strings, organized into five thematic concept clusters mapped to the manuscript's substantive sections, were executed using title/abstract [tiab] field tags and sorted by relevance:

Cluster 1 (senescence/SASP): (inflammaging OR inflamm-aging OR immunosenescence) AND (skin aging OR facial aging OR photoaging OR dermal aging)-67 records; (cellular senescence OR senescence-associated secretory phenotype OR SASP) AND (fibroblast OR keratinocyte OR dermis OR wound healing)-1,400 records.

Cluster 2 (MMP/TIMP, SMAS/fat): (matrix metalloproteinase OR MMP) AND (tissue inhibitor of metalloproteinase OR TIMP) AND (skin OR dermis OR aging)-571 records; (SMAS OR superficial musculoaponeurotic system OR facial fat compartment[s]) AND (aging OR inflammation)-259 records.

Cluster 3 (wound healing/macrophage/scarring): (macrophage polarization OR M1 M2 macrophage) AND wound healing AND (aging OR senescence)-16 records; (hypertrophic scar OR TGF-beta1 OR post-inflammatory hyperpigmentation) AND (aging OR senescence OR inflammation)-6,739 records.

Cluster 4 (energy-based devices): (fractional CO_2 OR ablative laser resurfacing) AND (aging OR elderly OR older adults) AND (efficacy OR complication OR erythema)-14 records; radiofrequency microneedling AND (fibrosis OR hyperpigmentation OR complication OR efficacy)-66 records; chemical peel AND (aging skin OR skin barrier OR wound healing)-23 records.

Cluster 5 (prehabilitation/senolytics/biomarkers): (prehabilitation OR senolytic[s]) AND (skin OR aesthetic OR surgery OR laser)-2,410 records; (exosome[s] OR Wharton's jelly OR peptide) AND (skin OR wound healing) AND (senescence OR aging)-563 records; (biomarker OR point-of-care) AND (IL-6 OR C-reactive protein OR cytokine) AND aging AND skin-10 records.

These twelve strings yielded 12,138 total database records. An additional 11 records were identified through citation chasing of reference lists in key reviews encountered during screening (4 in Cluster 2, 7 in Cluster 3), consistent with the supplementary "other sources" identification pathway of PRISMA-ScR.

Selection of sources of evidence. Because several search strings (most notably the broad senescence/SASP and hypertrophic-scar/TGF-β1 strings) returned several thousand records dominated by non-dermatologic disease contexts (oncology, pulmonary fibrosis, cardiac disease, orthopedics), exhaustive title/abstract screening of all 12,138 records was not feasible within the resources available for this review. A relevance-ranked screening protocol was therefore applied: for each search string, the first 40-50 relevance-ranked records (PubMed's default "best match" sort) were screened against the eligibility criteria above or the full record set where a search yielded fewer than the target screening depth. This is disclosed as a deliberate, resource-constrained rapid-review adaptation of standard scoping-review screening rather than an exhaustive census of the indexed literature, consistent with PRISMA-ScR's allowance for pragmatic, transparently reported screening approaches in broad or heterogeneous evidence domains. In total, 433 records were screened across the five thematic clusters (100 for the senescence/SASP cluster, 100 for the MMP/TIMP-SMAS/fat cluster, 66 for the wound-healing/macrophage cluster, 77 for the energy-device cluster and 90 for the prehabilitation/biomarker cluster), of which 333 were excluded, most commonly for addressing a non-cutaneous organ system or disease model, lacking an aging/senescence framing or duplicating the thematic content of an already-included,

higher-priority source. The 100 records retained after screening were combined with the 11 records identified via citation chasing for a total of 111 records assessed at the eligibility stage; one record (a lower-priority duplicate senescence commentary) was excluded at this final stage in favor of more specific, higher-yield sources, leaving 110 sources of evidence in the final synthesis. Post hoc verification confirmed no duplicate PMIDs among the 110 included sources.

Data Charting and Synthesis

For each included source, the reviewing team extracted author list, title, journal, year, volume/issue/pages, PMID and DOI, together with a structured statement of the source's key finding relevant to the review's thematic clusters. Findings were charted narratively by theme (cellular senescence/SASP; MMP/TIMP balance; SMAS/fat compartment anatomy; macrophage/wound-healing axis; pathologic cicatrization; energy-device and chemical-peel outcomes; prehabilitation, senolytics and biomarkers) rather than pooled quantitatively, consistent with the descriptive, evidence-mapping objective of a scoping review. No formal quality or risk-of-bias appraisal was performed, consistent with standard PRISMA-ScR guidance that critical appraisal is optional for scoping reviews.

Limitations of the Search Strategy

Three limitations are disclosed transparently rather than obscured. First, PubMed/MEDLINE was the only database searched; Embase, Scopus and gray-literature sources were not accessible or searched, which may have missed additional relevant records, particularly non-PubMed-indexed engineering/device literature. Second, the relevance-ranked screening cutoff, rather than exhaustive screening of all 12,138 raw hits, is a pragmatic adaptation that may have missed lower-ranked but relevant records, particularly in the broad senescence/SASP and hypertrophic-scar clusters. Third and most substantively, this search strategy itself surfaced a genuine evidentiary gap rather than merely a search-strategy artifact: age-stratified device-outcome data (Cluster 4) and validated point-of-care inflammaging biomarkers in aesthetic populations (Cluster 5, Search 3) are both objectively sparse in the indexed literature, a finding that directly supports, rather than undermines, this review's Section IX ("Future Directions and Research Gaps") argument.

Results: Study Selection and Characteristics

Fig. 1 presents the PRISMA-ScR flow diagram summarizing source identification, screening, eligibility and inclusion. Of 12,149 records identified (12,138 through database searching and 11 through citation chasing), 433 were screened, 333 were excluded and 111 were assessed at the eligibility stage; 110 were included in the final narrative synthesis (Table 1).

The 110 included sources spanned publication years 1988-2026, with a pronounced concentration in the past decade reflecting the recency of cellular senescence and SASP as an active research area. Sources included foundational mechanistic reviews and primary laboratory studies (cellular senescence, SASP, MMP/TIMP biology), facial anatomy and histology studies (SMAS, retaining ligaments, fat compartments), clinical case series, cohort studies and systematic reviews/meta-analyses (energy-device and chemical-peel outcomes) and mechanistic or early-phase clinical trials (senolytics, exosomes, peptides, nutraceuticals). Nineteen sources addressed cellular senescence and the SASP directly (Section V-A); 20 addressed MMP/TIMP balance and facial structural anatomy (Sections V-B and V-C); 21 addressed the macrophage axis, epithelialization and pathologic cicatrization (Section VI); 24 addressed energy-based device and chemical-peel outcomes (Section VII); and 26 addressed prehabilitation, senolytics, regenerative biomaterials and biomarkers (Sections VIII and IX).

Thematic Cluster	Manuscript Section	Records Screened	Records Excluded	Sources Included
Cellular senescence and SASP	V-A	100	80	19
MMP/TIMP balance; SMAS and fat compartments	V-B, V-C	100	84	20
Macrophage axis, epithelialization and scarring	VI	66	52	21

Energy-based devices and chemical peels	VII	77	53	24
Prehabilitation, senolytics and biomarkers	VIII, IX	90	64	26
Total		**433**	**333**	**110**

Table 1: Summary of included sources of evidence by thematic cluster.

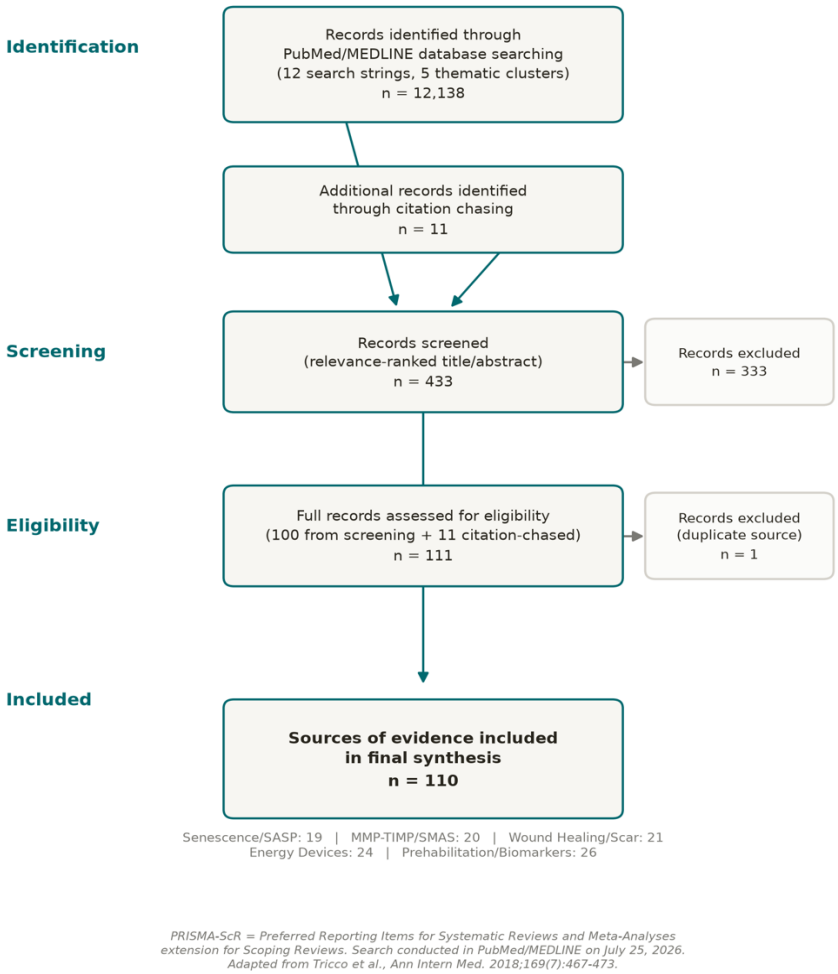

Figure 1: PRISMA-ScR flow diagram summarizing identification, screening, eligibility and inclusion of sources of evidence.

Pathophysiology of Inflammaging in the Aging Face

Cellular Senescence and the Senescence-Associated Secretory Phenotype

At the cellular level, the principal engine of inflammaging is cellular senescence: a state of stable, essentially irreversible cell-cycle arrest triggered by diverse intrinsic and extrinsic stressors, including telomere attrition, DNA damage, oncogene activation, oxidative stress and mitochondrial dysfunction [6]. Senescent cells resist apoptosis and instead adopt a Senescence-Associated Secretory Phenotype (SASP), a complex, context-dependent secretome comprising pro-inflammatory cytokines, chemokines, matrix metalloproteinases and growth factors [7]. Critically, the SASP is not intrinsically pathological: transiently senescent fibroblasts and endothelial cells recruited to a cutaneous wound accelerate closure and myofibroblast differentiation through secretion of PDGF-AA, demonstrating that the acute SASP serves an adaptive, reparative function in tissue remodeling and wound healing [7]. Pathology arises when senescent cells and their secretory output accumulate chronically rather than resolve, a shift that appears to occur progressively with chronological age and is accelerated by cumulative environmental insult, most notably ultraviolet radiation [8].

Within the skin specifically, senescent cells accumulate heterogeneously across compartments and cell types. Dermal fibroblasts, keratinocytes and melanocytes each exhibit distinct senescence phenotypes and secretory programs and their crosstalk with skin-resident immune cells (Langerhans cells, dendritic cells, T cells, innate lymphoid cells) reshapes the local immune microenvironment in ways that predispose aged skin to both impaired barrier function and inflammatory dermatoses [9,10]. Single-cell transcriptomic and spatial mapping studies have refined this picture considerably, showing that senescent reticular dermal fibroblasts are specifically associated with diminished collagen and elastic fiber synthesis, while senescent epidermal melanocytes correlate with dysregulated pigmentation and that photoaged skin carries a substantially higher senescent-cell burden than chronologically aged skin alone, directly implicating cumulative UV exposure as an accelerant of the senescent/SASP burden relevant to facial aging and, by extension, aesthetic surgical planning [11]. Cytokine and chemokine signaling constitute the principal intercellular communication axis by which these senescent cell populations exert paracrine effects on neighboring keratinocytes, fibroblasts and infiltrating immune cells, propagating a self-reinforcing cycle of local chronic inflammation, extracellular matrix degradation and further senescence induction [12,13].

Mitochondrial dysfunction has emerged as both a cause and consequence of cutaneous cellular senescence, forming a mechanistic node connecting bioenergetic decline to inflammatory secretory programming. Loss of mitochondrial integrity (through reduced NAD+/NADH ratios, increased reactive oxygen species and release of mitochondrial DNA into the cytosol) activates the cGAS-STING and NF-κB signaling pathways, driving a specific "Mitochondrial Dysfunction-Associated Senescence" (MiDAS) phenotype with a distinctive, IL-1-independent SASP signature [14]. In human dermal fibroblasts, deficiency of Carnitine Acetyltransferase (CRAT), found to be downregulated in intrinsically aged skin, recapitulates this mitochondrial-senescence axis, producing oxidative stress, disrupted mitochondrial morphology, a metabolic shift toward glycolysis and consequent SASP secretion with reduced collagen density *in-vivo* [15]. These findings position mitochondrial dysfunction alongside genomic instability and telomere attrition as core, mechanistically interlinked hallmarks of aging that converge on the dermal fibroblast as a central effector cell of cutaneous inflammaging [16,17].

Taken together, this body of evidence supports a coherent pathophysiological model in which senescent dermal fibroblasts and keratinocytes, activated by cumulative intrinsic (mitochondrial, genomic) and extrinsic (UV, pollution) stressors, secrete a chronic SASP that maintains the local cutaneous microenvironment in a persistent low-grade "alarm" state. This local inflammaging, compounded by concurrent systemic immunosenescence, manifests clinically as impaired barrier function, reduced dermal collagen and elastin content, delayed wound healing and the visible phenotypes of facial and dermal aging that are of direct relevance to plastic and aesthetic surgical practice [18,19]. Emerging senotherapeutic strategies, senolytics that selectively clear senescent cells and SASP inhibitors that blunt their secretory output, represent a mechanistically grounded, though still early-stage, translational avenue for mitigating inflammaging-driven skin aging and may inform future adjuncts to surgical and non-surgical rejuvenation approaches, a theme this review revisits in Section VIII [20].

Matrix Metalloproteinases versus Tissue Inhibitors of Metalloproteinases

Skin homeostasis depends on a dynamic equilibrium between Extracellular Matrix (ECM) synthesis and its enzymatic turnover by Matrix Metalloproteinases (MMPs), a family of zinc-dependent endopeptidases capable of degrading essentially every structural component of the dermis, including fibrillar collagens, elastin, fibronectin and proteoglycans [21]. Under physiologic conditions, MMP activity is tightly restrained by Tissue Inhibitors of Metalloproteinases (TIMPs), a four-member family (TIMP-1 through TIMP-4) that binds MMPs with near-stoichiometric, subnanomolar affinity [22]. Aging and chronic low-grade inflammation disrupt this equilibrium bidirectionally: MMP expression rises while TIMP expression and function decline, producing a net catabolic shift that progressively degrades the dermal collagen and elastin network [21,2].

The collagenolytic arm of this imbalance is best characterized for MMP-1, the primary initiator of type I and III collagen fibril cleavage in human skin. Dermal fibroblasts in chronologically aged skin (>80 years) express significantly higher levels of MMP-1 than fibroblasts in young skin, driven by elevated AP-1 transcriptional activity and $\alpha 2\beta 1$ integrin signaling [23]. Critically, this is not a static lesion but a self-amplifying cycle: MMP-1-mediated collagen fragmentation reduces the mechanical tension that fibroblasts sense through the ECM and fibroblasts cultured on fragmented collagen respond by producing even more MMP-1, AP-1 and Reactive Oxygen Species (ROS), which further upregulate MMP-1 expression [23]. This feedback loop couples oxidative stress directly to progressive collagen loss, extending the oxidative theory of skin aging beyond a purely cell-intrinsic phenomenon to encompass the ECM microenvironment itself. Downstream, cleaved collagen fragments are further processed by stromelysins (MMP-3) and gelatinases (MMP-9), compounding the structural damage [21]. Elastin turnover follows an analogous but mechanistically distinct pathway: macrophage- and fibroblast-derived MMP-12 (macrophage metalloelastase) is

the principal elastase responsible for elastic fiber degradation and its expression is inducibly and specifically upregulated in human skin by UVA1 irradiation, directly linking chronic environmental/inflammatory insult to the accumulation of dystrophic elastotic material characteristic of solar elastosis [21,24].

The inhibitory, TIMP-dependent side of this balance is equally compromised with age. TIMP-1 expression declines with fibroblast senescence both in *ex-vivo* culture and *in-vivo*, removing a key restraint on MMP-1, MMP-2 and MMP-3 activity within the dermis [22]. Aged human skin also fails to mount the normal injury-induced upregulation of TIMP-1 and TIMP-2 seen in younger tissue, such that TIMP mRNA remains at low, unstimulated basal levels throughout the wound-healing time course in older subjects [25]. The clinical consequence is a dermal environment structurally predisposed to unchecked proteolysis, both at baseline and following any inflammatory or traumatic stimulus that is a state that parallels the chronic proteolytic dysregulation described in non-healing wounds, where MMP expression persists unopposed by adequate TIMP-1 counter-regulation [26]. Direct clinical evidence for extrinsic acceleration of this catabolic shift comes from a demonstration that smokers exhibit significantly elevated MMP-1 mRNA in buttock (non-photoexposed) skin relative to non-smokers, with no compensatory rise in TIMP-1-establishing that chronic subclinical inflammatory or oxidative exposure, independent of UV radiation, is sufficient to tilt the MMP/TIMP ratio toward degradation [27].

At the cellular level, this imbalance is increasingly understood to be actively orchestrated by senescent dermal fibroblasts rather than merely reflecting passive enzymatic drift. Senescent fibroblasts adopt a SASP, releasing not only MMPs but pro-inflammatory cytokines such as IL-6 and IL-8, which paracrine-signal to keratinocytes, endothelium and adjacent adipocytes, propagating a self-sustaining, low-grade inflammatory microenvironment that further impairs matrix homeostasis and structurally resembles the pathological milieu of chronic, poorly healing wounds [26,28]. This SASP-driven catabolic microenvironment is the cellular substrate connecting the histologic MMP/TIMP imbalance to the systemic concept of inflammaging and cross-tissue evidence from intervertebral disc degeneration confirms that an analogous age-related rise in the MMP-to-TIMP ratio drives progressive connective-tissue breakdown in other collagen-rich structures, reinforcing this as a generalizable, tissue-independent mechanism of aging-associated matrix loss [29].

Impact on the SMAS and Facial Fat Compartments

Facial aging is not confined to the epidermis and papillary dermis; it extends to the deeper structural scaffold comprising the Superficial Musculoaponeurotic System (SMAS), the retaining ligaments and the compartmentalized facial fat that these structures support. The SMAS is a continuous fibromuscular fascial layer investing the mimetic musculature of the face and its integrity-together with that of the retaining ligaments that tether it to the underlying periosteum and deep fascia-is what physically opposes gravitational descent of the soft-tissue envelope [30,31]. Direct histological evidence of age-related SMAS degeneration comes from immunohistochemical and micro-CT analysis of surgical SMAS specimens, which identified alterations in collagen type III content, vascular density and periosteal fixation architecture at the ligamentous attachment points-providing biomarker-level confirmation that the SMAS undergoes measurable structural remodeling with age, analogous to the collagen degradation documented in the dermis proper [32]. Clinically, the loss of ligamentous and SMAS support manifests as the two cardinal signs of facial aging: descent of the malar fat pad, which deepens the nasolabial fold and accentuates the tear-trough deformity and the formation of jowls that obscure the mandibular border [33]. Surgical series confirm the structural relevance of this ligamentous attenuation: reconstruction of retaining ligaments beneath the SMAS significantly reduces the rate of early relapse of aging signs after facelift, indicating that the durability of surgical rejuvenation is directly tied to the biomechanical integrity of these support structures [34].

The facial fat compartments-discrete, septum-bounded units of superficial and deep adipose tissue first delineated anatomically over the past two decades-undergo their own compartment-specific, age-dependent volumetric changes rather than aging as a uniform mass [35,36]. These compartments are histologically heterogeneous: fibrous-type fat (perioral), structural-type fat (midface) and deposit-type fat (buccal and deep temporal pads) differ in adipocyte size and in the collagenous composition of their surrounding ECM, which dictates their differing mechanical and volumetric behavior with age [37]. The deep medial cheek, nasolabial, superficial middle and lateral cheek compartments are preferentially susceptible to deflation, while deep compartments-which structurally support the superficial layers and overlying SMAS-provide a scaffold whose loss disproportionately drives the regional, non-uniform contour changes recognized clinically as facial aging [36,38].

Mechanistically, this compartmental fat loss is now understood to be an active, biologically driven process rather than passive volumetric attrition and chronic low-grade inflammation is central to that process. Aging white adipose tissue undergoes a well-

characterized dysfunctional transition marked by increased secretion of pro-inflammatory adipokines, decreased anti-inflammatory mediators, impaired preadipocyte differentiation, oxidative and mitochondrial stress, reduced vascularization, increased fibrosis and accumulation of senescent cells-a constellation that both reflects and amplifies the systemic pro-inflammatory state of inflammaging [39]. Emerging evidence indicates that this adipocyte dysfunction is not merely a downstream consequence of skin and soft-tissue aging but may act as an upstream driver: senescent adipocytes within skin-associated (particularly dermal white) adipose tissue adopt their own SASP, undergo metabolic reprogramming and alter adipokine secretion in ways that directly promote dermal ECM deterioration and fibroblast dysfunction, forming an adipocyte-immune-fibroblast signaling network that amplifies tissue-level aging phenotypes across the dermal-subcutaneous interface [40]. This adipocyte-centered mechanism provides a unifying pathophysiological link between the chronic inflammatory, MMP/TIMP-imbalanced dermal microenvironment described above and the structural attenuation of the SMAS, retaining ligaments and facial fat compartments that together define the clinical phenotype of the aging face-supporting a model in which inflammaging acts as a shared upstream driver of both dermal matrix loss and deep structural facial descent, with direct implications for the sequencing and durability of aesthetic surgical and volumetric interventions [32,39,40].

Impact of Inflammaging on Tissue Repair and Scar Formation

Cutaneous wound healing is a temporally choreographed sequence of hemostasis, inflammation, proliferation and remodeling and its fidelity depends on the orderly resolution of each phase before the next begins [41]. In the aged or chronically inflamed host, this choreography is disrupted at nearly every level, producing a phenotype of delayed, qualitatively altered repair that is directly relevant to the incisional and post-procedural healing seen in aesthetic and reconstructive surgery patients. Three interlocking mechanisms-disruption of the macrophage polarization axis, redox- and protease-driven blunting of epithelialization and angiogenesis and TGF-β1-mediated pathologic cicatrization-together constitute the tissue-repair face of inflammaging.

Disruption of the Macrophage Axis

Macrophages are the principal orchestrators of the transition from destructive to reparative wound biology, normally shifting from a pro-inflammatory M1 phenotype (clearing pathogens and debris) to an anti-inflammatory, pro-regenerative M2 phenotype that supports angiogenesis and matrix deposition [42]. Aging disturbs this plasticity at the cellular level: macrophages harvested from aged hosts show blunted induction of both M1 markers (iNOS, IL-1β, TNF-α) and M2 markers (Arg1, Ym1, FIZZ1) upon stimulation, indicating that senescent macrophages lose the responsiveness required for a clean phenotypic switch rather than simply defaulting to one pole [43]. Compounding this, the aged tissue microenvironment as a whole tends toward an M2-dominant, yet functionally unresolved, inflammatory state, in which macrophage behavior is polarized but the resolution of inflammation that should accompany M2 dominance fails to occur-paradoxically impairing rather than accelerating healing [42]. This is corroborated by human hypertrophic scar biopsy data showing a delayed but prolonged infiltration of type-2 macrophages relative to normotrophic scars, evidence that the macrophage transition is not merely slowed but temporally decoupled from the surrounding tissue repair program [44]. Senescent stromal cells actively participate in this dysregulation: senescent dermal fibroblasts secrete IL-33 as part of their SASP and this SASP factor directly modulates local macrophage polarization, illustrating a feed-forward loop in which senescent cells recruited to injury sites shape-and can distort-the macrophage program governing repair [45]. The broader immunosenescence literature frames this at the systems level: healthy aging is characterized by elevated circulating pro-inflammatory cytokines (TNF, IL-1β, IL-6) alongside a compensatory rise in anti-inflammatory mediators including TGF-β1 and IL-10 and this imbalance of pro- and anti-inflammatory signaling is proposed to be a central determinant of dysregulated macrophage-driven injury repair in older patients [46]. Pharmacologic proof-of-concept supports the causal importance of this axis: agents that force M2 polarization via AMPK/mTOR/NLRP3 inflammasome inhibition measurably accelerate wound closure and angiogenesis, indicating that restoring normal macrophage transition kinetics is sufficient to improve healing outcomes even without correcting upstream aging biology [47]. Clinically, this translates to the well-established observation that wound healing in older patients is delayed rather than categorically defective, with comorbidities compounding-but not fully explaining-age-intrinsic deficits in the immune choreography of repair [48].

Epithelialization and Angiogenesis

A second axis of inflammaging's impact on tissue repair operates through oxidative and proteolytic stress that directly blunts the two processes most visible to the surgeon: wound closure (re-epithelialization) and revascularization (angiogenesis). Reactive Oxygen Species (ROS), when inadequately detoxified by antioxidant enzyme systems such as catalase, superoxide dismutase

and glutathione peroxidase, are implicated in the pathogenesis of non-healing wounds, an effect disproportionately observed in aged individuals whose redox-buffering capacity is diminished [49]. This oxidative burden intersects with a parallel loss of protease regulation: MMPs must be expressed and activated within a narrow temporal window to permit controlled ECM degradation and keratinocyte migration across the wound bed and loss of this regulation-with excess, unchecked protease activity-is a defining biochemical signature of chronic, non-healing wounds [50]. Cellular senescence compounds this proteolytic and redox dysregulation at the structural level: aged dermal matrix becomes thinner, increasingly cross-linked and fragmented, with age-related increases in cellular senescence altering collagen fiber remodeling and tissue stiffness in ways that mechanobiologically impede the normal wound-healing trajectory independent of any single soluble mediator [51]. The clinical relevance of this senescence burden has been directly demonstrated: in human chronic wound biopsies, elevated expression of the senescence markers p21 (CDKN1A) and p16^INK4a^ predicts significantly longer time-to-healing, providing histopathologic confirmation that senescent-cell accumulation-not merely inflammatory signaling in isolation-measurably delays epithelialization in humans [52]. Reviews of the SASP further clarify that this relationship is double-edged: SASP factors can, in controlled amounts, promote tissue repair and regeneration, but their abnormal accumulation at injury sites in aged or metabolically compromised skin instead produces excessive inflammation, tissue dysfunction and wound intractability, reframing senescence not as inherently pathologic but as a process whose aging-associated dysregulation tips the balance toward impaired closure and revascularization [53]. Notably, reparative signaling extends beyond the dermis proper: subcutaneous white adipose tissue undergoes a "beiging" response after injury, secreting neuregulin-4 to regulate both macrophage polarization and myofibroblast function in support of angiogenic granulation tissue formation and this adipose-derived reparative signal is measurably suppressed in metabolically compromised (diabetic and by extension chronically inflamed or aged) wound states-identifying a further tissue compartment through which inflammaging can blunt vascular and epithelial repair [54].

Pathologic Cicatrization

The third and clinically most visible consequence of inflammaging in tissue repair is pathologic scar formation, mediated substantially through sustained TGF-β1 signaling. Under normal repair conditions, TGF-β1 drives the fibroblast-to-myofibroblast transition necessary for provisional matrix contraction and collagen deposition, but when inflammatory resolution fails-as occurs with aging-associated prolongation of the inflammatory phase-expansion of pro-fibrotic immune populations, including M2 macrophages, mast cells and Th2 cells, sustains TGF-β1 signaling well beyond its physiologic window, driving excessive fibroblast activation and pathologic collagen accumulation [55]. Mechanistically, this occurs through the canonical TGF-β/Smad signaling axis: sustained pathway activation produces long-term overactivation of fibroblasts and myofibroblasts that is necessary and sufficient for the excessive collagen formation characteristic of both keloid and hypertrophic scars, making this axis the principal molecular target for emerging antifibrotic therapeutics [56]. Classic plastic-surgery literature on hypertrophic scar pathogenesis situates this TGF-β1-driven fibrosis within a broader cascade of exaggerated inflammation, prolonged reepithelialization and dysregulated neovascularization and remodeling-all processes in which platelets, macrophages and keratinocytes participate directly-suggesting that pathologic cicatrization is best understood as a systems-level failure of inflammatory resolution rather than an isolated fibrotic event [57]. Comprehensive reviews of keloid and hypertrophic scar immunobiology reinforce that the character and magnitude, not merely the presence, of inflammation determines scar outcome, with continuous local inflammatory activity distinguishing pathologic from physiologic scarring [58]. The anti-inflammatory cytokine IL-10 has emerged as a counter-regulatory node in this pathway and its dysregulation is increasingly implicated in hypertrophic scar pathophysiology, offering a therapeutic lever distinct from direct TGF-β1 blockade [59].

For the aesthetic surgeon, prolonged incision-line erythema is a clinically observable proxy for this same unresolved inflammatory-fibrotic state, reflecting persistent vascular and inflammatory activity that, left unmodulated, predisposes to both hypertrophic scarring and, in an entirely separate but mechanistically related pathway, Post-Inflammatory Hyperpigmentation (PIH). PIH arises when cutaneous inflammation-whether from acne, laser resurfacing or surgical trauma-triggers increased melanin production and abnormal distribution via keratinocyte-melanocyte-fibroblast crosstalk and growth factor signaling, representing the pigmentary analog of TGF-β1-driven fibrotic cicatrization [60]. Enhanced or prolonged inflammatory responses have been directly implicated not only in PIH but in skin aging itself and this susceptibility is disproportionately relevant in darker skin phototypes commonly seen in diverse aesthetic surgery populations, where the inflammaging-PIH relationship carries outsized clinical and cosmetic consequences [61]. Taken together, the disruption of macrophage polarization kinetics, the redox/protease-driven blunting of epithelialization and angiogenesis and the TGF-β1-centered dysregulation of cicatrization constitute a mechanistically coherent, evidence-supported account of why inflammaging predisposes aesthetic and

reconstructive surgery patients to delayed healing, prolonged erythema, hypertrophic scarring and hyperpigmentation-underscoring the rationale for perioperative strategies that specifically target chronic low-grade inflammation and cellular senescence in the aging surgical patient.

The "Controlled Injury" Paradox: Impact on Advanced Modalities

Energy-based and chemical resurfacing modalities are predicated on a shared therapeutic logic: the deliberate infliction of controlled cutaneous injury to trigger a wound-healing cascade that culminates in re-epithelialization, dermal remodeling and neocollagenesis. This paradigm assumes a host tissue capable of mounting a coordinated, temporally appropriate inflammatory-proliferative-remodeling response. In the inflammaging phenotype-characterized by senescent fibroblast accumulation, blunted growth-factor signaling and chronic low-grade inflammatory tone-this assumption is frequently violated, producing a spectrum of efficacy shortfalls and complications that are disproportionately represented in aged and photodamaged hosts.

Ablative and Fractional CO_2 Resurfacing

The foundational wound-healing physiology of CO_2 laser resurfacing depends on rapid keratinocyte migration from adnexal reservoirs to re-establish epidermal continuity; under optimal (occluded, young) conditions this begins within 48 hours, whereas unoccluded or biologically compromised skin displays eschar formation and absent keratinocyte migration at the same interval, the histologic signature of delayed healing [62]. This mechanistic vulnerability is borne out clinically: case reports in aged patients-including a 77-year-old woman and a 55-year-old woman document that persistent erythema and in some cases, frank scarring occur even with fractionated (theoretically lower-morbidity) ablative devices, replicating complication profiles historically associated with traditional non-fractional resurfacing [63,64]. Notably, when aged, actinically damaged and atrophic skin (the bald, chronically sun-exposed scalp) was treated across three distinct modalities-medium-depth chemical peel, cryopeel and CO2 laser resurfacing-all three produced severely delayed wound healing and prolonged re-epithelialization regardless of the specific injury mechanism [65]. This convergence across mechanistically distinct modalities is strong indirect evidence that the substrate (aged, atrophic, chronically photodamaged skin), rather than device-specific parameters, is the dominant determinant of healing failure-a finding of direct relevance to any inflammaging framework.

Efficacy data further suggest that thermal injury does not reliably translate into proportionate structural gain in aged skin. A pilot study of ablative fractional CO_2 on photoaged dorsal hand skin achieved only 26-75% improvement across wrinkles, pigment and texture despite three treatment sessions, with one participant developing significant edema and long-term follow-up studies of fractional CO_2 for facial and neck photoaging, while demonstrating statistically significant and durable improvement, show a plateauing effect consistent with incomplete or self-limited neocollagenesis rather than progressive remodeling [66-68]. Perhaps most tellingly, a meta-analysis of laser combination therapies found that augmenting CO_2 resurfacing with radiofrequency energy failed to increase clinical improvement over CO_2 monotherapy while measurably prolonging erythema a direct demonstration that additional thermal/energy input in this class of modality can increase inflammatory burden without a compensatory gain in structural outcome, the essential signature of the controlled-injury paradox [69]. Clinical management studies confirm that erythema and prolonged downtime remain the dominant patient-experienced burden of fractional CO_2 resurfacing, with adjunctive anti-inflammatory topical regimens shown to shorten (but not eliminate) the erythema interval [70]. Broader systematic review data across nearly 1,100 patients situate ablative resurfacing as having a manageable but non-trivial adverse-event rate (approximately 8-10%) that must be interpreted cautiously, since the source literature seldom stratifies outcomes by chronological age or senescent burden [71,72].

Radiofrequency Microneedling

RF microneedling was developed in part to mitigate the epidermal risk of purely ablative modalities by sparing the stratum corneum while delivering thermal injury to the dermis via insulated or non-insulated needle electrodes. However, postmarketing surveillance data reveal that this modality carries its own distinctive complication signature. Analysis of FDA MAUDE reports spanning 2013-2025 identified 114 adverse-event reports encompassing 224 discrete events, the most frequent being textural change (25.0%) and pigmentary alteration (18.3%), followed by inflammatory reactions, burns and pain [73]. Textural change-clinically often described as a "waxy" or fibrotic surface quality-and pigmentary alteration are precisely the paradoxical outcomes of concern in aging/inflammaging hosts, where thermal injury delivered into a dermis already burdened by SASP activity may provoke disorganized, fibrotic collagen deposition rather than the orderly neocollagenesis observed in younger tissue. Mechanistic support for this concern comes from porcine histological modeling showing that higher-energy RF microneedling

modes (particularly bipolar configurations) produce greater thermal coagulation and more pronounced upregulation of TGF-β, MMP3 and elastin than lower-energy monopolar treatment-a molecular signature in which excessive or poorly titrated thermal load skews the repair program toward fibrosis [74]. Critical review of the highest-quality available RF microneedling trials concludes that induced dermal remodeling and neocollagenesis are "slow and progressive," continuing to evolve for at least six months post-treatment in a host with reduced fibroblast proliferative capacity, this prolonged remodeling window may never fully resolve into organized collagen, plausibly manifesting instead as the persistent textural change captured in postmarketing data [75].

Clinical efficacy studies in age-relevant populations reinforce this variability: in a cohort of 30 patients with a mean age of 55.5 years treated for lower-face and neck laxity, submental volume change ranged from a 26.65 cm^3 reduction to a 16.01 cm^3 increase-an extraordinarily wide range that signals substantial unpredictability of response in the precise population (aging, laxity-predominant) for whom the treatment is most commonly indicated [76]. Reviews addressing device parameters emphasize that needle depth and energy must be carefully titrated to anatomic subunit and, by extension, to the thinner, less compliant dermis characteristic of aged skin, since depth/energy mismatches are considered principal drivers of adverse textural and pigmentary sequelae [77,78]. Safety data in skin of color-a population with intrinsically heightened melanocyte reactivity-found transient postinflammatory hyperpigmentation in seven of thirty-five reviewed studies and one case each of prolonged hyperpigmentation and permanent scarring, illustrating that pigmentary risk, while generally described as low, is not negligible and may compound with the reduced melanocyte homeostatic reserve reported in chronologically aged epidermis [79]. Structured post-treatment skincare protocols have been shown to meaningfully improve patient-perceived redness and comfort, indicating that the erythema/textural burden of RF microneedling, while less severe than fully ablative resurfacing, remains clinically significant enough to warrant dedicated management protocols [80].

Chemical Peels

Chemical peeling occupies a unique position among controlled-injury modalities because peel depth is determined not by a fixed physical parameter (as with laser fluence) but by the interaction between a caustic agent's concentration/application technique and the biological properties of the substrate skin-properties that are demonstrably altered by aging. Foundational cutaneous physiology research demonstrates that aged skin (ages 69-85) exhibits significantly higher initial transepidermal water loss following barrier disruption and a markedly slower return to baseline (approximately double the relaxation time of young skin), meaning that the same peeling agent applied at an identical concentration may achieve a deeper, less predictable level of keratocoagulation and a substantially prolonged barrier-recovery interval in an aged patient compared with a younger one [81]. This barrier-recovery deficit provides direct mechanistic support for the clinical observation that peel depth is comparatively unpredictable in aging skin and that healing, once barrier integrity is breached, proceeds more slowly.

Clinical corroboration is again found in the actinic-keratosis/atrophic-scalp case series, in which a medium-depth chemical peel applied to severely photodamaged, atrophic skin produced the same severe healing delay observed with cryotherapy and CO_2 laser in the companion cases-directly implicating substrate quality rather than agent choice [65]. Systematic reviews of Trichloroacetic Acid (TCA) peeling for photoaging confirm meaningful cosmetic benefit at both superficial and medium-depth concentrations, but note that adverse events, although generally self-limited, occur across the available trial base and that concentration/technique standardization remains inconsistent between studies, limiting confidence in predicting peel depth a priori [82]. Older but methodologically instructive case literature in severely photodamaged, aged patients undergoing TCA chemexfoliation for extensive actinic damage found favorable cosmetic outcomes but explicitly tied this success to operator experience and careful patient selection, implicitly acknowledging that outcomes in less experienced hands or with less favorable substrate would be expected to diverge [83]. A comprehensive complications taxonomy of medium-depth and deep chemical peels situates persistent erythema, delayed healing, textural change and scarring as depth-dependent risks that escalate disproportionately once peels breach the papillary into the reticular dermis-the same anatomic plane in which age-related declines in dermal fibroblast density and collagen turnover are most pronounced [84]. Finally, experimental data demonstrate that adjunctive local anesthesia commonly used to improve patient comfort during peeling independently delays wound healing, an effect that appears unrelated to the vasoconstrictive properties of epinephrine-a clinically actionable but underappreciated compounding factor when peels are combined with adjunctive procedures in older surgical candidates [85].

Taken together, the ablative/fractional CO_2, RF microneedling and chemical peel literatures converge on a common theme directly relevant to the inflammaging framework: each modality's therapeutic mechanism depends on a wound-healing response whose kinetics, fidelity and structural output are measurably altered in aged skin, yet the majority of available efficacy and safety

literature does not explicitly stratify outcomes by chronological age, photoaging stage or senescent cellular burden. This represents both a genuine scientific gap and a call to future prospective, age-stratified investigation before the controlled-injury paradigm can be considered fully validated in the aging surgical candidate.

Aesthetic Prehabilitation: Optimizing the Host

The concept of prehabilitation-structured optimization of physiological reserve preceding an elective surgical stressor-is well established in general and oncologic surgery but remains almost entirely unexplored as a named construct in aesthetic and plastic surgery. A scoping review of surgical prehabilitation trials proposes a consolidated definition: a preoperative process combining exercise, nutrition, psychological support and respiratory training to enhance functional capacity prior to surgical stress [86]. This scaffold, though developed for oncologic and cardiac populations, is directly transferable to aesthetic surgery, where patients undergoing elective body contouring, facelift or combined procedures similarly have a defined preoperative window for host optimization. The strongest causal evidence comes from the international multicenter PREHAB randomized trial in colorectal cancer surgery, in which a four-week multimodal program reduced severe postoperative complications from 29.7% to 17.1% [87]. An umbrella review of 55 systematic reviews corroborates this signal, reporting low-to-moderate certainty evidence that exercise and nutritional prehabilitation reduce complications, non-home discharge and length of stay [88]. While none of this evidence derives from aesthetic populations, the rationale for extrapolation is strong: aesthetic surgery patients, like oncologic patients, undergo an elective, schedulable surgical insult superimposed on a baseline inflammaging trajectory and stand to benefit from analogous preoperative optimization.

Topical and Local Immunomodulation

Skin is now recognized as an active site of cellular senescence that contributes to and is shaped by, whole-body inflammaging. Senescent dermal and epidermal cells accumulate with chronological and photo-induced aging and secrete a SASP enriched in IL-6, IL-8, MMPs and other mediators [89,90]. Because this process is at least partially reversible, topical/local immunomodulation is the most mechanistically direct arm of aesthetic prehabilitation. Senolytic agents-most extensively Dasatinib-plus-Quercetin (D+Q)-reduce epidermal senescent cell burden and lower circulating SASP factors, including IL-6, IL-1α and MMP-9/12, within days of a brief "hit-and-run" dosing course in human pilot trials [91,92]. Translational work in hair follicle biology extends this logic: senolytic depletion of senescent dermal papilla cells reverses SASP accumulation and restores hair-inductive capacity, while IGF-1-driven follicle stem cell senescence is mitigated by senolytic treatment or dietary restriction in transgenic models [93,94]. Reviews of skin senotherapeutics-including one published directly in a core plastic surgery journal-frame senolytics/senomorphics as an emerging skincare class relevant to plastic surgical practice, while cautioning that translational challenges (cell-type heterogeneity, detection standardization) remain unresolved [95,96].

Adjacent to pharmacologic senolysis, regenerative biomaterials-exosomes and extracellular vesicles from mesenchymal stem cells, adipose tissue, platelets and umbilical cord (Wharton's jelly) tissue-have emerged as a major topical immunomodulatory strategy. MSC-derived exosomes exhibit anti-inflammatory, anti-aging and wound-healing bioactivity via cargo-dependent immune signaling and umbilical cord-derived MSC secretome exerts anti-inflammatory, anti-fibrotic, pro-angiogenic and anti-oxidative effects across all four wound-healing phases [97,98]. Clinical-grade evidence, though limited, is emerging: a randomized split-face trial combining adipose-derived exosome solution with microneedling significantly improved wrinkles, elasticity, hydration and pigmentation versus microneedling alone and a single-arm study of topical platelet-derived exosome serum showed six-week improvements in skin health score and redness [99,100]. Reviews corroborate mechanistic plausibility (reduced MMP expression, increased collagen/elastin) but caution that sourcing/storage variability and the absence of any FDA-approved exosome product limit standardization [101-104]. Peptide agents are a more regulatorily tractable parallel strategy: GHK-Cu suppresses NF-κB signaling while stimulating collagen/elastin synthesis and acetyl dipeptide-31 amide significantly reduced IL-4, IL-6, IL-8, IL-17 and TNF-α while increasing procollagen and hyaluronic acid, with 16-week clinical improvement in facial laxity [105,106]. A contemporary review of peptide mechanisms catalogues delivery-enhancement strategies (microneedling, iontophoresis, nanocarriers) to overcome poor stratum corneum permeability, the principal barrier for topical peptides [107].

Systemic and Metabolic Optimization

A second, complementary arm addresses systemic drivers of baseline inflammatory tone prior to surgery. Direct evidence in aesthetic-surgery patients is essentially absent; however, mechanistically adjacent data support nutraceutical/metabolic

intervention. A randomized trial of oral glucoraphanin and curcumin in healthy adults found eight days of supplementation reduced skin-biopsy expression of IL-1β, TNF-α, IL-6 and IL-17 while inducing cytoprotective NQO1 via the Keap1-Nrf2-ARE pathway-direct, biopsy-confirmed evidence that an oral regimen can modulate cutaneous inflammatory tone in humans [108]. This link is clinically consequential given the growing population of aesthetic candidates on GLP-1 receptor agonists: a review documents that GLP-1RA-induced adipose loss and altered adipose-derived stem cell function accelerate facial and skin aging, prompting adapted prehabilitative counseling and biostimulatory or fat-grafting strategies [109]. Although no literature addressing cortisol reduction, sleep optimization or standardized nutraceutical protocols preceding aesthetic surgery was identified, the senolytic pilot literature offers a precedent: intermittent "hit-and-run" dosing achieved measurable SASP reductions within 11 days suggesting short preoperative windows may suffice for systemic modulation even absent aesthetic-specific trial data [91,92].

Procedural Staging

No aesthetic-surgery-specific evidence on procedural staging as an inflammaging mitigation strategy was identified-an explicit gap rather than a synthesizable finding. Indirect support derives from the umbrella prehabilitation literature, where multimodal, time-extended (typically 3-4 week) preoperative windows were required to achieve measurable benefit, implying that unstaged aesthetic procedures lacking a defined optimization interval may forego an accessible risk-reduction opportunity [87,88]. The prehabilitation scoping review's framing of "the process from diagnosis to surgery" as the operative intervention window further supports staging elective aesthetic procedures to allow time for topical and systemic optimization before the surgical date [86].

Future Directions and Research Gaps

The most consequential finding of this literature search is negative: the biomarker-focused search string, designed to capture point-of-care or clinical biomarkers of inflammaging (IL-6, CRP, cytokine panels) in aging skin, returned only 10 total PubMed records, most addressing cognitive, epigenetic or non-cutaneous aging domains rather than validated dermatologic or perioperative biomarkers. This near-total absence of a mature point-of-care biomarker literature for aesthetic-surgery-relevant inflammaging is itself a central research gap this review is positioned to articulate. The few salvageable signals are instructive but preliminary: serum MMP9, alongside high-sensitivity CRP, rises significantly with normal chronological aging and has been proposed as an accessible inflammaging biomarker, though its behavior diverges in accelerated-aging syndromes such as Werner syndrome, underscoring limited generalizability across aging phenotypes [110]. Similarly, exploratory data from the first-in-human senolytic pilot trial in idiopathic pulmonary fibrosis found physical-function improvements correlated with reductions in SASP-related proteins and cytokines in roughly half the markers assayed, though the authors characterized these effects as "inconclusive" [111]. No study identified validated a point-of-care assay for preoperative risk stratification or prehabilitation-response monitoring in aesthetic candidates. Future research should prioritize rapid-turnaround biomarker panels-combining circulating cytokines (IL-6, TNF-α), matrix remodeling enzymes (MMP-9) and skin senescence markers (p16, p21)-deployable in outpatient clinics to stratify baseline inflammaging burden and quantify prehabilitative response.

A second major gap concerns protocol standardization. The surgical prehabilitation field only recently converged on a consensus definition after reviewing 76 randomized trials and finding prehabilitation explicitly defined in barely half [86]. Aesthetic surgery lags further behind: no citation identified operationalizes "aesthetic prehabilitation" as a distinct, named pathway with defined duration, components or outcome measures-with direct implications for IRB trial design. Investigators testing prehabilitation, senolytic or nutraceutical interventions in aesthetic populations currently have no field-specific template and must extrapolate from oncologic/cardiac trials or from senolytic dosing regimens validated in diabetic kidney disease and pulmonary fibrosis rather than cosmetic surgery candidates [87,88,92,111]. A clear priority is registration of the first dedicated aesthetic-surgery prehabilitation RCT, incorporating topical senomorphic/exosome-based preparation, systemic nutraceutical support and staged procedural timing with prespecified inflammaging biomarker endpoints.

A third gap concerns the sparse age-stratification of the energy-device literature described in Section VII: relatively few of the 24 device-outcome sources identified explicitly compared aged versus young skin within the same protocol and the strongest historical evidence for age-modified healing kinetics in ablative resurfacing derives from case reports and mechanistic studies from the 1990s and 2000s rather than contemporary controlled trials [62-64]. Prospective trials of ablative, fractional and RF-based modalities that explicitly stratify outcomes by chronological age, Glogau photoaging stage or a validated senescence biomarker are needed before the controlled-injury paradigm described in Section VII can be considered fully evidence-based in the aging surgical candidate.

Finally, the role of regenerative biomaterials and senolytics in clearing senescent cells from aesthetic surgery patients specifically-versus preclinical or non-aesthetic disease models-remains largely theoretical. Current exosome/MSC-secretome literature, while mechanistically compelling and supported by small clinical trials in cosmetic dermatology is limited by sourcing, isolation and storage variability and by the absence of any regulatory-approved exosome therapeutic [99,100,102]. Senolytic agents, despite strong mechanistic rationale and encouraging early-phase safety data elsewhere have not been tested as a preoperative adjunct to reduce senescent cell burden before an aesthetic procedure [91,92,111]. Given that intermittent senolytic dosing has already demonstrated feasibility and measurable SASP reduction within an 11-day window in other populations, a phase 1 feasibility trial of short-course preoperative senolytic dosing before elective aesthetic surgery-with biopsy-confirmed senescent cell clearance and wound-healing tracking-represents a tractable next step [92]. Collectively, these gaps in objective biomarkers, standardized protocols and aesthetic-specific senolytic/regenerative data define the translational frontier that must be prioritized before "aesthetic prehabilitation" matures from conceptual extrapolation into evidence-based clinical standard.

Discussion

This scoping review maps, for the first time, a coherent pathophysiological through-line connecting systemic inflammaging biology to four domains of direct relevance to aesthetic and reconstructive surgical practice. Cellular senescence and the SASP (Section V-A) provide the molecular engine; MMP/TIMP imbalance and SMAS/fat compartment attenuation (Sections V-B, V-C) provide the structural readout in the aging face; disrupted macrophage polarization and TGF-β1-driven cicatrization (Section VI) provide the mechanistic link to impaired healing after any incisional or ablative intervention; and the controlled-injury literature on energy-based devices and chemical peels (Section VII) provides indirect but consistent clinical corroboration that this biology manifests as disproportionate erythema, unpredictable neocollagenesis and textural or pigmentary complications in aged and photodamaged patients. The prehabilitation literature (Section VIII) and its associated research gaps (Section IX) then define where the field must go next: from documenting inflammaging as a passive risk factor to actively modulating it as a preoperative, protocolized intervention.

Several caveats temper this synthesis. First and most importantly, direct evidence linking cellular senescence or SASP burden to aesthetic surgical outcomes specifically is largely absent; the model presented here is built by connecting adjacent, individually well-supported literatures (senescence biology, wound-healing immunology, device-outcomes case series) rather than by citing a single unified aesthetic-surgery inflammaging cohort study, because no such study yet exists. Second, the device-outcomes literature reviewed in Section VII, while clinically informative, is dominated by case reports, pilot studies and reviews that do not stratify by age or senescent burden, meaning the "controlled injury paradox" as applied to energy-based devices remains a well-supported hypothesis rather than a directly demonstrated causal relationship. Third, this review's own search strategy-PubMed-only, relevance-ranked screening rather than exhaustive review of all 12,138 raw records and a July 2026 search date-may have missed additional relevant sources, particularly non-PubMed-indexed engineering, device-industry or non-English literature; these limitations are disclosed in Section III rather than minimized. Fourth, the near-absence of validated biomarkers and standardized "aesthetic prehabilitation" protocols documented in Section IX means that, at present, no evidence-based algorithm exists for identifying which patients would benefit most from preoperative senolytic, regenerative or metabolic optimization or for how long such optimization should be applied before an elective procedure.

Despite these caveats, the practical implication for the practicing aesthetic surgeon is a shift in framing rather than an immediately actionable protocol: the host tissue bed should be considered a modifiable biological variable, not a fixed anatomic given. In the near term, this may translate into more conservative energy/depth titration and explicit preoperative counseling about prolonged erythema or unpredictable neocollagenesis in older or heavily photodamaged patients undergoing energy-based resurfacing (Section VII); consideration of staged rather than single-session aggressive combination procedures in this population (Section VIII-C); and cautious, informed-consent-based use of topical senotherapeutics, peptides or regenerative biomaterials as adjuncts where mechanistic rationale is strong even though direct aesthetic-surgery outcome data remain limited (Section VIII-A). In the longer term, the research agenda outlined in Section IX-age-stratified device trials, validated point-of-care inflammaging biomarkers and a registered aesthetic-prehabilitation randomized trial-represents the evidentiary bridge required before host-tissue optimization can move from a biologically plausible concept to a standard of care.

Conclusion

Inflammaging reframes the aging face not as an inert anatomic substrate but as the visible output of an active, chronic, low-grade inflammatory process rooted in cellular senescence and its secretory phenotype. This review's synthesis of 110 sources across

five thematic domains supports a mechanistically coherent model in which senescent dermal, adipocyte and immune cell populations drive MMP/TIMP imbalance, SMAS and fat-compartment attenuation, stalled macrophage-mediated wound repair and TGF-β1-driven pathologic scarring-a biology that plausibly, though not yet directly, explains the disproportionate complications observed when controlled-injury aesthetic modalities are applied to aged and photodamaged skin. "Aesthetic prehabilitation"-the deliberate, preoperative modulation of this inflammaging biology through topical senotherapeutics, regenerative biomaterials, systemic metabolic optimization and procedural staging-is conceptually well grounded in adjacent surgical prehabilitation evidence but remains almost entirely untested as a named, protocolized intervention specific to aesthetic surgery. Closing this gap will require standardized aesthetic-prehabilitation trial definitions, validated point-of-care inflammaging biomarkers and age- and senescence-stratified device-outcome studies. Until then, the central message for the practicing aesthetic surgeon is one of paradigm shift rather than immediate protocol change: durable, complication-free rejuvenation depends not only on correcting the anatomic defect, but on optimizing the biological host in which that correction must heal.

Conflict of Interest

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Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not applicable.

Authors' Contributions

Both authors conceived the review, designed the search strategy, screened and synthesized the literature and drafted and revised the manuscript collaboratively.

References

1. Tricco AC, Lillie E, Zarin W. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-473.
2. Karpuzoglu E, Holladay SD, Gogal RM Jr. Inflammaging: triggers, molecular mechanisms, immunological consequences, sex differences and cutaneous manifestations. Front Immunol. 2025;16:1704203.
3. Pająk J, Nowicka D, Szepietowski JC. Inflammaging and immunosenescence as part of skin aging-a narrative review. Int J Mol Sci. 2023;24(9):7784.
4. Salminen A. Clinical perspectives on the age-related increase of immunosuppressive activity. J Mol Med (Berl). 2022;100(5):697-712.
5. Zhuang Y, Lyga J. Inflammaging in skin and other tissues-the roles of complement system and macrophage. Inflamm Allergy Drug Targets. 2014;13(3):153-161.
6. He S, Sharpless NE. Senescence in health and disease. Cell. 2017;169(6):1000-1011.
7. Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell. 2014;31(6):722-733.
8. Salminen A, Kaarniranta K, Kauppinen A. Photoaging: UV radiation-induced inflammation and immunosuppression accelerate the aging process in the skin. Inflamm Res. 2022;71(7-8):817-831.
9. Lee YI, Choi S, Roh WS, Lee JH, Kim TG. Cellular senescence and inflammaging in the skin microenvironment. Int J Mol Sci. 2021;22(8):3849.

10. Chen B, Yang J, Song Y, Zhang D, Hao F. Skin immunosenescence and type 2 inflammation: a mini-review with an inflammaging perspective. Front Cell Dev Biol. 2022;10:835675.
11. Yu GT, Ganier C, Allison DB, Tchkonia T, Khosla S, Kirkland JL, et al. Mapping epidermal and dermal cellular senescence in human skin aging. Aging Cell. 2025;24(1):e14358.
12. Lin ZC, Hsu CY, Hwang E, Wang PW, Fang JY. The role of cytokines/chemokines in an aging skin immune microenvironment. Mech Ageing Dev. 2023;210:111761.
13. Zhang J, Yu H, Man MQ, Hu L. Aging in the dermis: fibroblast senescence and its significance. Aging Cell. 2024;23(2):e14054.
14. Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Freund A, et al. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metab. 2016;23(2):303-314.
15. Song MJ, Park CH, Kim H, Han S, Lee SH, Lee DH, et al. Carnitine acetyltransferase deficiency mediates mitochondrial dysfunction-induced cellular senescence in dermal fibroblasts. Aging Cell. 2023;22(11):e14000.
16. Wyles SP, Maredia HS, Ansaf RB, Dweydari MR, Hurt RT, Bonnes SL, et al. Skinspan™: a healthy longevity framework for skin aging. Mayo Clin Proc. 2025;100(11):1976-1991.
17. Ho CY, Dreesen O. Faces of cellular senescence in skin aging. Mech Ageing Dev. 2021;198:111525.
18. Waaijer MEC, Goldeck D, Gunn DA, van Heemst D, Westendorp RGJ, Pawelec G, et al. Are skin senescence and immunosenescence linked within individuals? Aging Cell. 2019;18(4):e12956.
19. He R, Sun M, Liu T, Geng L, Xing C, Xu P, et al. Hallmarks of the aging skin microenvironment: components and mechanisms. J Cell Physiol. 2025;240(11):e70111.
20. Gasek NS, Kuchel GA, Kirkland JL, Xu M. Strategies for targeting senescent cells in human disease. Nat Aging. 2021;1(10):870-879.
21. Pittayapruek P, Meephansan J, Prapapan O, Komine M, Ohtsuki M. Role of matrix metalloproteinases in photoaging and photocarcinogenesis. Int J Mol Sci. 2016;17(6):868.
22. Hornebeck W. Down-regulation of tissue inhibitor of matrix metalloprotease-1 (TIMP-1) in aged human skin contributes to matrix degradation and impaired cell growth and survival. Pathol Biol (Paris). 2003;51(10):569-573.
23. Fisher GJ, Quan T, Purohit T, Shao Y, Cho MK, He T, et al. Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. Am J Pathol. 2009;174(1):101-114.
24. Tewari A, Grys K, Kollet J, Sarkany R, Young AR. Upregulation of MMP12 and its activity by UVA1 in human skin: potential implications for photoaging. J Invest Dermatol. 2014;134(10):2598-2609.
25. Ashcroft GS, Herrick SE, Tarnuzzer RW, Horan MA, Schultz GS, Ferguson MW. Human ageing impairs injury-induced in vivo expression of tissue inhibitor of metalloproteinases (TIMP)-1 and -2 proteins and mRNA. J Pathol. 1997;183(2):169-176.
26. Saarialho-Kere UK. Patterns of matrix metalloproteinase and TIMP expression in chronic ulcers. Arch Dermatol Res. 1998;290(Suppl):S47-S54.
27. Lahmann C, Bergemann J, Harrison G, Young AR. Matrix metalloproteinase-1 and skin ageing in smokers. Lancet. 2001;357(9260):935-936.
28. Zheng J, Wang S, Sun J, Lv J. Dermal fibroblast senescence: the central hub of skin aging-from intrinsic dysfunction to microenvironmental remodeling. Int J Mol Sci. 2026;27(4):1653.
29. Vo NV, Hartman RA, Yurube T, Jacobs LJ, Sowa GA, Kang JD. Expression and regulation of metalloproteinases and their inhibitors in intervertebral disc aging and degeneration. Spine J. 2013;13(3):331-341.
30. Whitney ZB, Jain M, Zito PM. Anatomy, skin, superficial musculoaponeurotic system (SMAS) fascia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan 30-.
31. Alghoul M, Codner MA. Retaining ligaments of the face: review of anatomy and clinical applications. Aesthet Surg J. 2013;33(6):769-782.
32. Hînganu MV, Cucu RP, Costan VV, Lozneanu L, Tamaș C, Calistru AE, et al. Aging of superficial musculoaponeurotic system of the face-novel biomarkers and micro-CT relevance of facial anti-gravity support. Diagnostics (Basel). 2024;14(11):1126.
33. Charafeddine AH, Zins JE. The extended superficial musculoaponeurotic system. Clin Plast Surg. 2019;46(4):533-546.
34. Bitik O. Sub-SMAS reconstruction of retaining ligaments. Aesthet Surg J. 2022;42(11):1207-1217.
35. Ramanadham SR, Rohrich RJ. Newer understanding of specific anatomic targets in the aging face as applied to injectables: superficial and deep facial fat compartments-an evolving target for site-specific facial augmentation. Plast Reconstr Surg. 2015;136(5 Suppl):49S-55S.
36. Rohrich RJ, Avashia YJ, Savetsky IL. Prediction of facial aging using the facial fat compartments. Plast Reconstr Surg. 2021;147(1S-2):38S-42S.
37. Kruglikov I, Trujillo O, Kristen Q, Isac K, Zorko J, Fam M, et al. The facial adipose tissue: a revision. Facial Plast Surg. 2016;32(6):671-682.
38. Stuzin JM, Rohrich RJ, Dayan E. The facial fat compartments revisited: clinical relevance to subcutaneous dissection and facial deflation in face lifting. Plast Reconstr Surg. 2019;144(5):1070-1078.
39. Zamboni M, Nori N, Brunelli A, Zoico E. How does adipose tissue contribute to inflammageing? Exp Gerontol. 2021;143:111162.
40. Wang E, Xu Z, Wang Y, Wang J, Jiang Y, Zhao C. Adipocytes as core drivers of skin aging and novel targets for regeneration. Biogerontology. 2026;27(2):65.
41. Mony MP, Harmon KA, Hess R, Dorafshar AH, Shafikhani SH. An updated review of hypertrophic scarring. Cells. 2023;12(5):678.
42. Goh J, Ladiges WC. Exercise enhances wound healing and prevents cancer progression during aging by targeting macrophage polarity. Mech Ageing Dev. 2014;139:41-48.

43. Mahbub S, Deburghgraeve CR, Kovacs EJ. Advanced age impairs macrophage polarization. J Interferon Cytokine Res. 2012;32(1):18-26.
44. van den Broek LJ, van der Veer WM, de Jong EH, Gibbs S, Niessen FB. Suppressed inflammatory gene expression during human hypertrophic scar compared to normotrophic scar formation. Exp Dermatol. 2015;24(8):623-629.
45. Chen Y, Ma L, Cheng Z. Senescent fibroblast facilitates re-epithelization and collagen deposition in radiation-induced skin injury through IL-33-mediated macrophage polarization. J Transl Med. 2024;22(1):176.
46. Duong L, Radley HG, Lee B. Macrophage function in the elderly and impact on injury repair and cancer. Immun Ageing. 2021;18(1):4.
47. Qing L, Fu J, Wu P, Zhou Z, Yu F, Tang J. Metformin induces the M2 macrophage polarization to accelerate the wound healing via regulating AMPK/mTOR/NLRP3 inflammasome signaling pathway. Am J Transl Res. 2019;11(2):655-668.
48. Kremer M, Burkemper N. Aging skin and wound healing. Clin Geriatr Med. 2024;40(1):1-10.
49. Schäfer M, Werner S. Oxidative stress in normal and impaired wound repair. Pharmacol Res. 2008;58(2):165-171.
50. Caley MP, Martins VL, O'Toole EA. Metalloproteinases and wound healing. Adv Wound Care (New Rochelle). 2015;4(4):225-234.
51. Blair MJ, Jones JD, Woessner AE, Quinn KP. Skin structure-function relationships and the wound healing response to intrinsic aging. Adv Wound Care (New Rochelle). 2020;9(3):127-143.
52. Yu GT, Gomez PT, Prata LG. Clinicopathological and cellular senescence biomarkers in chronic stalled wounds. Int J Dermatol. 2024;63(9):1227-1235.
53. Kita A, Yamamoto S, Saito Y, Chikenji TS. Cellular senescence and wound healing in aged and diabetic skin. Front Physiol. 2024;15:1344116.
54. Cai J, Quan Y, Zhu S. The browning and mobilization of subcutaneous white adipose tissue supports efficient skin repair. Cell Metab. 2024;36(6):1287-1301.e7.
55. Hong YK, Chang YH, Lin YC, Chen B, Guevara BEK, Hsu CK. Inflammation in wound healing and pathological scarring. Adv Wound Care (New Rochelle). 2023;12(5):288-300.
56. Zhang T, Wang XF, Wang ZC. Current potential therapeutic strategies targeting the TGF-β/Smad signaling pathway to attenuate keloid and hypertrophic scar formation. Biomed Pharmacother. 2020;129:110287.
57. van der Veer WM, Bloemen MCT, Ulrich MMW. Potential cellular and molecular causes of hypertrophic scar formation. Burns. 2009;35(1):15-29.
58. Wang ZC, Zhao WY, Cao Y. The roles of inflammation in keloid and hypertrophic scars. Front Immunol. 2020;11:603187.
59. Sun ZL, Feng Y, Zou ML. Emerging role of IL-10 in hypertrophic scars. Front Med (Lausanne). 2020;7:438.
60. Maghfour J, Olayinka J, Hamzavi IH, Mohammad TF. A focused review on the pathophysiology of post-inflammatory hyperpigmentation. Pigment Cell Melanoma Res. 2022;35(3):320-327.
61. Markiewicz E, Karaman-Jurukovska N, Mammone T, Idowu OC. Post-inflammatory hyperpigmentation in dark skin: molecular mechanism and skincare implications. Clin Cosmet Investig Dermatol. 2022;15:2555-2565.
62. Collawn SS. Re-epithelialization of the skin following CO_2 laser resurfacing. J Cosmet Laser Ther. 2001;3(3):123-127.
63. Fuchs D, Querings K, Burg G, Böni R. Persistent erythema after total CO_2 skin resurfacing. Schweiz Med Wochenschr. 1999;129(21):813-817.
64. Behar Ross R, Spencer J. Scarring and persistent erythema after fractionated ablative CO_2 laser resurfacing. J Drugs Dermatol. 2008;7(11):1072-1073.
65. Quaedvlieg PJF, Ostertag JU, Krekels GA, Neumann HAM. Delayed wound healing after three different treatments for widespread actinic keratosis on the atrophic bald scalp. Dermatol Surg. 2003;29(10):1052-1056.
66. Stebbins WG, Hanke CW. Ablative fractional CO_2 resurfacing for photoaging of the hands: pilot study of 10 patients. Dermatol Ther. 2011;24(1):62-70.
67. Tan J, Lei Y, Ouyang HW, Gold MH. The use of fractional CO2 laser resurfacing in the treatment of photoaging in Asians: five years long-term results. Lasers Surg Med. 2014;46(10):750-756.
68. Oram Y, Akkaya AD. Neck rejuvenation with fractional CO_2 laser: long-term results. J Clin Aesthet Dermatol. 2014;7(8):23-29.
69. Pour Mohammad A, Gholizadeh Mesgarha M, Seirafianpour F, Karimi Y, Sodagar S, Afraie M, et al. A systematic review and meta-analysis of efficacy, safety and satisfaction rates of laser combination treatments vs laser monotherapy in skin rejuvenation resurfacing. Lasers Med Sci. 2023;38(1):228.
70. Zoccali G, Cinque B, La Torre C, Lombardi F, Palumbo P, Romano L, Mattei A, Orsini G, Cifone MG, Giuliani M. Improving the outcome of fractional CO2 laser resurfacing using a probiotic skin cream: preliminary clinical evaluation. Lasers Med Sci. 2016;31(8):1607-1611.
71. Mirza HN, Mirza FN, Khatri KA. Outcomes and adverse effects of ablative vs nonablative lasers for skin resurfacing: a systematic review of 1093 patients. Dermatol Ther. 2021;34(1):e14432.
72. Rinaldi F. Laser: a review. Clin Dermatol. 2008;26(6):590-601.
73. Chou M, Myers B, Avram M. Analysis of US Food and Drug Administration data on radiofrequency microneedling device complications. Dermatol Surg. 2026.
74. Wang H, Hamblin MR, Zhang Y, Xu Y, Wen X. Histological evaluation of monopolar and bipolar radiofrequency microneedling treatment in a porcine model. Lasers Surg Med. 2024;56(3):288-297.
75. Tan MG, Jo CE, Chapas A, Khetarpal S, Dover JS. Radiofrequency microneedling: a comprehensive and critical review. Dermatol Surg. 2021;47(6):755-61.

76. Nguyen L, Blessmann M, Schneider SW, Herberger K. Radiofrequency Microneedling for Skin Tightening of the Lower Face, Jawline and Neck Region. Dermatol Surg. 2022;48(12):1299-305.
77. Shauly O, Marxen T, Menon A, Gould DJ, Miller LB, Losken A. Radiofrequency microneedling: Technology, devices and indications in the modern plastic surgery practice. Aesthet Surg J Open Forum. 2023;5:ojad100.
78. Weiner SF. Radiofrequency microneedling: Overview of Technology, advantages, differences in devices, studies and indications. Facial Plast Surg Clin North Am. 2019;27(3):291-303.
79. Syder NC, Chen A, Elbuluk N. Radiofrequency and radiofrequency microneedling in skin of color: A review of usage, safety and efficacy. Dermatol Surg. 2023;49(5):489-93.
80. Grieshaber E, Glorioso A. An open-label study assessing the efficacy and tolerability of a post-treatment skincare protocol following radiofrequency microneedling for facial rejuvenation. J Clin Aesthet Dermatol. 2022;15(5):12-8.
81. Roskos KV, Guy RH. Assessment of skin barrier function using transepidermal water loss: effect of age. Pharm Res. 1989;6(11):949-53.
82. Sitohang IBS, Legiawati L, Suseno LS, Safira FD. Trichloroacetic acid peeling for treating photoaging: A systematic review. Dermatol Res Pract. 2021;2021:3085670.
83. Brodland DG, Roenigk RK. Trichloroacetic acid chemexfoliation (chemical peel) for extensive premalignant actinic damage of the face and scalp. Mayo Clin Proc. 1988;63(9):887-96.
84. Nikalji N, Godse K, Sakhiya J, Patil S, Nadkarni N. Complications of medium depth and deep chemical peels. J Cutan Aesthet Surg. 2012;5(4):254-60.
85. Davies B, Guyuron B, Husami T. The role of lidocaine, epinephrine and flap elevation in wound healing after chemical peel. Ann Plast Surg. 1991;26(3):273-278.
86. Fleurent-Grégoire C, Burgess N, McIsaac DI, Chevalier S, Fiore JF Jr, Carli F, et al. Towards a common definition of surgical prehabilitation: a scoping review of randomised trials. Br J Anaesth. 2024;133(2):305-15.
87. Molenaar CJL, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi R, et al. Effect of multimodal prehabilitation on reducing postoperative complications and enhancing functional capacity following colorectal cancer surgery: The PREHAB randomized clinical trial. JAMA Surg. 2023;158(6):572-81.
88. McIsaac DI, Gill M, Boland L, Hutton B, Branje K, Shaw J, et al. Prehabilitation in adult patients undergoing surgery: an umbrella review of systematic reviews. Br J Anaesth. 2022;128(2):244-57.
89. Franco AC, Aveleira C, Cavadas C. Skin senescence: mechanisms and impact on whole-body aging. Trends Mol Med. 2022;28(2):97-109.
90. Thau H, Gerjol BP, Hahn K. Senescence as a molecular target in skin aging and disease. Ageing Res Rev. 2025;105:102686.
91. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020;288(5):518-36.
92. Hickson LJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, et al. Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine. 2019;47:446-56.
93. Pappalardo A, Kim JY, Abaci HE, Christiano AM. Restoration of hair follicle inductive properties by depletion of senescent cells. Aging Cell. 2025;24(1):e14353.
94. Wang Y, Yang J, Luo Y, Zhao Z, Yuan Y, Li J, et al. Targeting IGF1-induced cellular senescence to rejuvenate hair follicle aging. Aging Cell. 2025;24(7):e70053.
95. Pils V, Ring N, Valdivieso K, Lämmermann I, Gruber F, Schosserer M, et al. Promises and challenges of senolytics in skin regeneration, pathology and ageing. Mech Ageing Dev. 2021;200:111588.
96. Lee BP, Harries LW. Senotherapeutic Drugs: A New Avenue for Skincare? Plast Reconstr Surg. 2021;148(6S):21S-26S.
97. Ha DH, Kim HK, Lee J, Kwon HH, Park GH, Yang SH, et al. Mesenchymal stem/stromal cell-derived exosomes for immunomodulatory therapeutics and skin regeneration. Cells. 2020;9(5):1157.
98. Li X, Zhang D, Yu Y, Wang L, Zhao M. Umbilical cord-derived mesenchymal stem cell secretome promotes skin regeneration and rejuvenation: From mechanism to therapeutics. Cell Prolif. 2024;57(4):e13586.
99. Park GH, Kwon HH, Seok J, Yang SH, Lee J, Park BC, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study. J Cosmet Dermatol. 2023;22(12):3418-26.
100. Proffer SL, Paradise CR, DeGrazia E. Efficacy and Tolerability of Topical Platelet Exosomes for Skin Rejuvenation: Six-Week Results. Aesthet Surg J. 2022;42(10):1185-93.
101. Hajialiasgary Najafabadi A, Soheilifar MH, Masoudi-Khoram N. Exosomes in skin photoaging: biological functions and therapeutic opportunity. Cell Commun Signal. 2024;22(1):32.
102. Vyas KS, Kaufman J, Munavalli GS, Robertson K, Behfar A, Wyles SP. Exosomes: the latest in regenerative aesthetics. Regen Med. 2023;18(2):181-94.
103. Dan X, Li S, Chen H, Xue P, Liu B, Ju Y, et al. Tailoring biomaterials for skin anti-aging. Mater Today Bio. 2024;28:101210.
104. Xiong M, Zhang Q, Hu W, Zhao C, Lv W, Yi Y, et al. The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics. Pharmacol Res. 2021;166:105490.
105. Pickart L, Margolina A. Regenerative and protective actions of the GHK-Cu peptide in the light of the new gene data. Int J Mol Sci.

2018;19(7):1987.
106. Edison BL, Parsa R, Dufort M, Tierney NK, Green BA, Farris PK. Acetyl dipeptide-31 amide: A novel cosmetic anti-inflammatory peptide that demonstrates anti-aging, firming and lifting benefits. J Drugs Dermatol. 2025;24(1):23-33.
107. Pintea A, Manea A, Pintea C, Vlad RA, Bîrsan M, Antonoaea P, et al. Peptides: Emerging candidates for the prevention and treatment of skin senescence: A review. Biomolecules. 2025;15(1):88.
108. Chien AL, Liu H, Rachidi S. Oral glucoraphanin and curcumin supplements modulate key cytoprotective enzymes in the skin of healthy human subjects: A randomized trial. Metabolites. 2025;15(6):360.
109. Ridha Z, Fabi SG, Zubar R, Dayan SH. Decoding the implications of glucagon-like peptide-1 receptor agonists on accelerated facial and skin aging. Aesthet Surg J. 2024;44(11):NP809-N18.
110. Goto M, Chiba J, Matsuura M, Iwaki-Egawa S, Watanabe Y. Inflammageing assessed by MMP9 in normal Japanese individuals and the patients with Werner syndrome. Intractable Rare Dis Res. 2016;5(2):103-8.
111. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine. 2019;40:554-63.

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