Beyond Melanin Clearance: Melanocyte–Fibroblast Crosstalk and Stromal Matrix Responses to Pigment-Targeted Laser Exposure

A Critical Translational Review

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Abstract

The biological consequences of pigment-targeted laser exposure extend beyond visible melanin reduction. The iris stroma is a multicellular microenvironment containing melanocytes, fibroblasts and other stromal cells, vascular and immune populations, and extracellular matrix (ECM). Human iris co-culture studies demonstrate fibroblast-dependent regulation of melanogenic activity, while tissue immunohistochemistry and cell-resolved atlases identify endogenous matrix-regulatory proteins and distinct stromal cell populations. Historical human histopathology following Nd:YAG iridotomy and argon peripheral iridoplasty further documents procedure-dependent patterns of stromal disruption, pigment-bearing cellular responses, fibroblast-like proliferation, and collagen alteration. These findings cannot be transferred directly to selective anterior stromal melanin modulation because the laser mechanisms, exposure architectures and tissue targets differ. This critical translational review integrates human iris evidence with experimental iris-laser histology and clearly distinguished analogies from dermal fibroblast and trabecular-meshwork research. It examines four analytically distinct domains: melanosome modification, melanocyte viability and function, melanocyte–fibroblast signalling, and ECM organisation and turnover. An evidence-stratified experimental agenda is proposed, combining cell-specific assays, protein- and matrix-level measurements, and longitudinal structural assessment. Separating the visible pigmentary endpoint from the biological state of the residual stroma provides a testable basis for future protocol-specific studies.

Keywords: iris stroma; melanocyte; fibroblast; pigment-targeted laser; extracellular matrix; paracrine signalling; stromal remodeling; ocular histopathology; macrophage; anterior segment optical coherence tomography (AS-OCT)

1. Introduction

Discussions of iris depigmentation generally converge on visible colour, liberated pigment, intraocular pressure, and anterior-chamber response. Those outcomes are clinically important, but they do not fully describe what occurs within the irradiated stromal microenvironment. An apparently lighter iris may arise through altered pigment content, altered optical presentation, loss of pigmented organelles, changes in cell pigmentation, or combinations of these phenomena. None is automatically equivalent to the loss of melanocytes or disruption of collagen-rich stromal architecture.

A biologically useful analysis therefore separates the primary interaction between laser energy and melanin from subsequent responses of pigment-bearing cells, non-melanocytic stromal populations, and the surrounding extracellular matrix (ECM). These compartments are physically connected but are not interchangeable experimental endpoints. Selective photothermolysis provides a mechanism for preferential energy deposition in pigmented targets; it does not, by itself, prove that every adjacent cell and structural component remains unchanged after a given exposure [1].

This review addresses the post-exposure microenvironment rather than downstream clearance through the anterior chamber. Its central question is whether apparently similar pigmentary endpoints could coexist with distinct patterns of melanocyte viability, local paracrine activity, and stromal matrix response. The goal is an anatomically specific and falsifiable research agenda, not a new treatment score or a claim of clinical superiority.

2. Scope and approach to evidence

This is a critical, non-systematic translational review based on targeted PubMed and original publisher-record searches and backward reference checking conducted in October 2026. Searches emphasised human iris stromal melanocytes, fibroblast signalling, matrix metalloproteinases, single-cell mapping, and pigment-directed laser responses. The selection was purposive rather than exhaustive, with no registered protocol or formal risk-of-bias assessment. The evidence selected for analysis spans human iris morphology and co-culture experiments, immunostaining of normal human

anterior-uveal tissue, a single-cell atlas of adult human iris, an experimental rabbit iris-laser study, and mechanistic laser studies performed in other tissues. Sources were evaluated according to their tissue of origin, exposure model, measured outcome, and relevance to a human iris application. The article makes no claim of exhaustive literature retrieval or quantitative synthesis; a formal systematic review would require a registered search and risk-of-bias protocol.

Throughout the text, “direct iris evidence” denotes observations generated in native or cultured iris tissue, whereas “cross-tissue analogy” denotes findings from skin fibroblasts, trabecular-meshwork cells, or other experimental systems. Findings in one exposure architecture cannot be transferred to another solely because both target pigmentation.

3. Iris colour, melanocyte number, and pigment content represent different variables

Human histological studies provide a necessary starting point. Wilkerson and colleagues, in an analysis of 51 human irides, found no statistically significant relation between visible iris colour and stromal melanocyte counts or density [2]. Prota and colleagues independently demonstrated differences in melanin quantity and composition across iris tissues, including compositional distinctions between stromal fractions and posterior iris pigment epithelium [3]. These observations argue against using apparent iris colour as a surrogate for the number or viability of stromal melanocytes.

The distinction becomes even more important after pigment-targeted energy delivery. Melanosome alteration, cellular depigmentation, and melanocyte death are mechanistically and analytically separable. A change in melanosome load within surviving cells might yield optical changes that differ from those produced by removal or loss of pigment-containing cells. Tissue-level imaging alone is generally insufficient to distinguish these endpoints, particularly when scattering, pupil diameter, and imaging conditions also influence the apparent colour.

The classical principle of selective photothermolysis supports organelle-specific photothermal targeting under suitable optical and temporal conditions [1]. Nevertheless, the structural and biological consequences depend on the actual deposited energy, subcellular location, tissue geometry, and cumulative exposure. One cannot infer preservation—or destruction—of adjacent structures from the concept of selectivity alone.

4. The iris stroma is a multicellular regulatory microenvironment

Human iris stroma contains more than pigment-bearing melanocytes. A 2022 single-nucleus atlas of the human anterior segment, spanning tissues from six donors, identified diverse cell classes within the iris [13]. A 2025 single-cell analysis integrating three adult donor irides subsequently distinguished melanocytic stroma, non-melanocytic stroma, macrophage/immune-associated cells, vascular populations, and iris muscle as distinct transcriptomic identities [4]. The melanocytic cluster expressed pigmentation-associated genes including MLANA and DCT, whereas the non-melanocytic stromal population included developmental and structural markers such as FOXC1 and PITX2. These data provide an anatomical and molecular reference map, not a post-laser response map.

That distinction is central. The presence of a cell population or an expressed gene in untreated iris tissue establishes potential biological capacity, not activation after exposure. Transcript abundance also cannot by itself demonstrate secreted protein abundance, enzyme activity, or tissue mechanics. Even so, a cell-resolved reference helps define which populations and pathways should be sampled when exposure-response studies become feasible.

The stromal response should therefore be considered at multiple levels: pigment organelles inside melanocytes; melanocyte stress, survival, and melanogenic competence; signalling between melanocytes and neighbouring stromal cells; and extracellular-matrix composition and organisation. These need not evolve in parallel.

5. Human evidence for melanocyte–fibroblast signalling

A distinctive feature of human ocular pigmentation biology is the experimentally demonstrated dependence of melanogenic activity on neighbouring cells. Smith-Thomas and colleagues reported increased dopa oxidase activity when cultured ocular melanocytes were co-cultured with fibroblasts or epithelial cells, supporting regulation by the cellular microenvironment [5]. This was not an investigation of laser exposure; it established that melanocyte function is not exclusively cell-autonomous.

A subsequent human iris co-culture study supplied a more specific mechanistic example. Latanoprost and prostaglandin F2α induced a convincing melanogenic response in iridial melanocytes in the presence of fibroblasts, whereas monocultured melanocytes responded inconsistently. FP-receptor expression was observed in fibroblasts but not cultured iridial melanocytes, leading the authors to propose an indirect fibroblast-mediated pathway [6]. Although these

pharmacological findings cannot predict post-laser behaviour, they establish an experimentally tractable iris-specific principle: perturbation of neighbouring stromal cells can modify melanocyte function.

For pigment-directed laser research, the relevant unanswered question is not simply whether residual melanocytes are alive, but whether their interaction with the surrounding cells remains functionally equivalent to baseline. Candidate readouts include melanogenesis markers, secreted paracrine mediators, cell viability, and functional response to established stimuli. Candidate mediators such as stem cell factor (SCF), hepatocyte growth factor (HGF), and fibroblast growth factor 2 (FGF2) may be considered because they are implicated in other melanocyte–fibroblast contexts; their post-laser induction in human iris stroma must be demonstrated rather than assumed.

6. Direct iris laser observations and the limits of inference

Direct iris-laser experiments provide a tissue-specific reference for interpreting pigment-associated responses. In a rabbit model, Yildirim and colleagues studied surface-directed 532-nm laser exposure and reported altered anterior stromal pigmentation and pigment-laden histiocytes [7]. The findings demonstrate histologically detectable changes in an experimental iris but do not quantify human stromal signalling or matrix turnover.

Human observations provide stronger anatomical specificity while revealing substantial differences between laser modalities. Goldberg, Tso, and Mirolovich examined two human iridectomy specimens after full-thickness Nd:YAG iridotomy and documented stromal and vascular necrosis consistent with mechanical disruption, without the thermal pattern of argon photocoagulation [16]. In a late follow-up series, Tetsumoto and colleagues examined three human iridotomy specimens obtained 3–5 years after Nd:YAG exposure; pigment-bearing stromal cells were present, while sampled sites lacked fibrous scarring [14]. The small number of specimens and the full-thickness iridotomy context limit extrapolation to superficial pigment modification.

In contrast, Sassani and colleagues investigated two human eyes following argon laser peripheral iridoplasty. Histology obtained 16 days after treatment demonstrated contraction furrows, fibroblast-like cell proliferation, surface collagen deposition, stromal collagen denaturation, and coagulative vascular necrosis [17]. These findings are direct evidence that some laser exposures can induce fibrocellular and matrix-associated responses in human iris tissue, but represent thermal peripheral iridoplasty rather than selective anterior stromal depigmentation.

Grimaldos Ruiz described a preliminary histological investigation involving 100 cadaver eyes, performed to compare iris pigment distributions and the effects of four laser systems before clinical photoablative cosmetic iridoplasty [18]. Although this work is anatomically relevant, the clinical publication does not provide a matched longitudinal human stromal molecular dataset that would resolve melanocyte survival, cytokine secretion, or ECM remodelling after exposure. Taken together, these human and experimental studies establish biological plausibility and protocol dependence, not a common molecular response shared by all iris lasers.

Table 1. Direct human iris laser histopathology and protocol-specific interpretation.

Study and tissue	Laser / design	Directly reported histopathology	Interpretive boundary
Goldberg et al., 1987 [16] 2 human iridectomy specimens	Nd:YAG iridotomy; full-thickness defects	Mechanical disruption with stromal and vascular necrosis; no thermal-type changes identified.	Not a selective superficial pigment protocol; does not establish post-depigmentation molecular fate.
Tetsumoto et al., 1992 [14] 3 human iridectomy specimens	Nd:YAG iridotomy; sampling 3–5 years later	Pigment-laden stromal cells and loose cellular margins; no fibrous scarring or inflammatory response in sampled sites.	Late, small iridotomy series; absence of scar is not general evidence of stromal recovery in other protocols.
Sassani et al., 1993 [17] 2 eyes, 1 patient	Argon peripheral iridoplasty; tissue sampled at day 16	Fibroblast-like proliferation, surface collagen deposition, stromal collagen denaturation, vascular necrosis.	Thermal peripheral iridoplasty; tissue response cannot be assigned to selective melanin modification.
Grimaldos Ruiz, 2021 [18] 100 cadaver eyes reported	Comparison of four lasers described within a clinical publication	Cadaver-eye histology / laser-effect assessment reported; detailed cellular signalling / ECM assays not shown.	Descriptive report does not quantify post-exposure stromal molecular mechanisms in living human eyes.

FIGURE 2

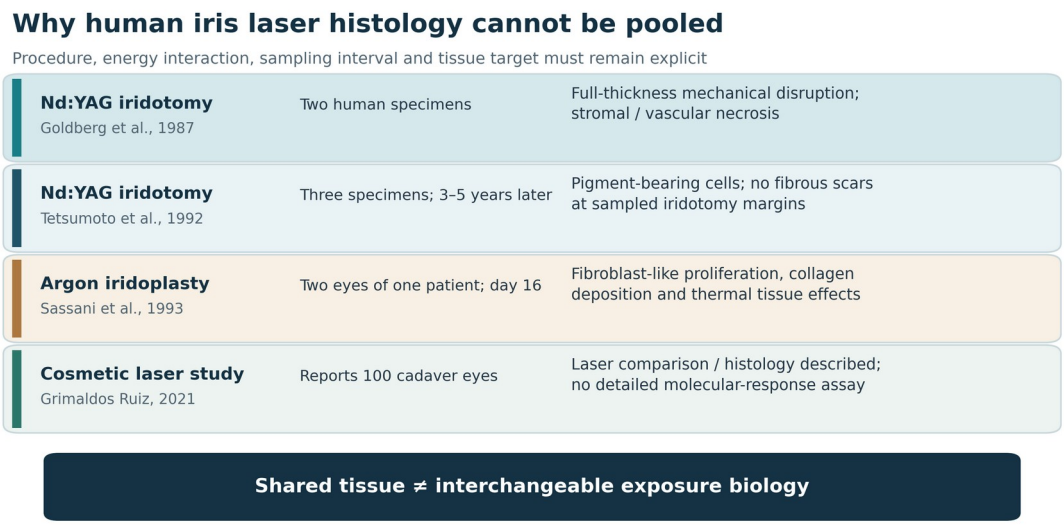

Figure 2. Procedure-specific human iris histopathology. The depicted laser settings and tissue responses originate from distinct reports and must not be interpreted as outcomes of a single pigment-reduction protocol.

7. Cross-tissue evidence: laser energy can change cell signalling without a simple structural endpoint

Two lines of experimental literature strengthen biological plausibility while setting important limits. First, in cultured human dermal fibroblasts, sublethal 532-nm Q-switched laser exposure altered melanogenesis-related gene expression, with increased secretion of selected factors such as SCF and bFGF in responsive cell cultures and affected contraction of fibroblast-populated collagen lattices [8,9]. Poon and colleagues observed delayed collagen-lattice contraction despite no significant difference in collagen synthesis under their conditions [8]. This demonstrates why collagen production and functional matrix behaviour should be evaluated separately. It does not establish an analogous iris effect.

Second, Shimizu and colleagues exposed melanin-loaded human trabecular-meshwork cells to micropulse laser irradiation and found early cytokine responses, subsequent increases in several MMP transcripts, and changes in collagen I and fibronectin expression, with pigmentation modifying the response [10]. The laser–pigment interaction in this study was situated in an outflow tissue with distinct cellular architecture, exposure pattern, and function. Extrapolation to iris stroma would be inappropriate without direct experiments, but the work identifies a relevant methodological strategy: measure pigment density, early cell signalling, later matrix-related changes, and tissue-specific functional outcomes as separate variables.

The broader histopathological literature on pigment-directed dermatological lasers further distinguishes organelle-level pigment effects from cumulative melanocyte dysfunction [11]. Again, the appropriate transfer is the experimental distinction—not an assumed direction or magnitude of effect in the iris.

8. ECM homeostasis in the normal human anterior uvea

The ECM is not merely a passive scaffold around iris pigment cells. Lan and colleagues demonstrated immunoreactivity for MMP-1, MMP-2, MMP-3, MMP-9, and TIMP-1 through TIMP-4 in human iris and ciliary-body tissue, with prominent staining in the anterior border and anterior epithelial region and additional staining around stromal vessels [12]. These observations demonstrate an endogenous ECM-regulatory protein repertoire in native iris tissue, while not proving enzyme activation after laser exposure. A historical human case report also documented ectopically proliferating iris stromal melanocytes associated with newly deposited collagen and basement-membrane material [15]; because this was a pathological setting, it does not establish normal melanocyte behaviour or any response to depigmentation.

MMP and TIMP expression, enzymatic activation, collagen abundance, collagen organisation, and tissue stiffness are different endpoints. For example, an increase in MMP messenger RNA does not necessarily translate into a proportional change in active proteolysis; compensating inhibitors and matrix synthesis may modify the result. Similarly, altered

lattice contraction in a fibroblast culture cannot be equated with a clinical reduction in iris rigidity. A rigorous stromal study must avoid inferring biomechanical dysfunction from a single molecular marker.

9. Separating organelle, cellular, and matrix endpoints

The proposed synthesis is deliberately modest. It does not introduce a numerical risk scale or a new diagnostic classification. Instead, it specifies four experimentally separable domains: pigment-organelle response; melanocyte viability and phenotype; stromal paracrine signalling; and matrix architecture and function. Their relationships may be causal, correlated, compensatory, or absent. The distinction is useful precisely because simultaneous change should not be presumed.

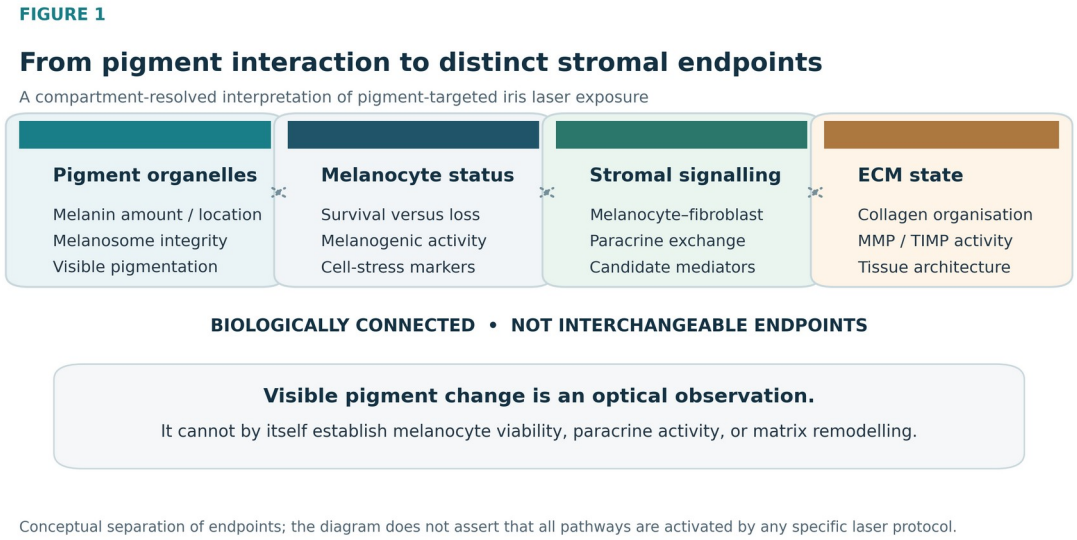

Figure 1. Distinct biological domains at the irradiated stromal site. Changes in melanin, melanocyte function, stromal signalling and matrix organisation are related but must be assessed independently.

Table 2. Evidence provenance and limits of transfer across tissue models.

Evidence context	What the cited work establishes	Not established by this evidence
Human iris morphology [2,3]	Iris colour does not reliably index melanocyte counts; pigment composition differs by compartment.	Post-laser cell survival and ECM architecture.
Human iris co-culture [5,6]	Fibroblast presence can influence melanogenic response to pharmacological stimuli.	That pigment laser exposure activates the same signalling.
Normal iris cell / protein atlases [4,12,13]	Distinct stromal populations; MMP and TIMP immunoreactivity in normal tissue.	Post-laser ECM enzyme activity or specific recovery kinetics.
Rabbit pigment-targeted iris laser [7]	Histological iris pigment / tissue changes after a defined experimental exposure.	Human protocol-specific response or long-term functional outcomes.
Laser-treated dermal fibroblasts [8,9]	Paracrine-expression and collagen-lattice changes in skin-derived cells.	Equivalent changes in iris fibroblasts.
Pigmented trabecular-meshwork cells [10]	Inflammatory / matrix-related readouts following defined laser treatment in another ocular tissue.	Direct iris stromal cytokine or ECM response.

The domains also require explicit negative controls. Absence of visible tissue thinning does not exclude biochemical change; a detectable cytokine response does not, by itself, constitute pathology; and loss of pigment does not establish melanocyte loss. Conversely, the absence of a clinical complication in an observed series cannot settle these mechanistic questions.

10. Prospective and ex vivo research design: measurable endpoints

The most informative near-term experimental design would pair baseline tissue characterisation with controlled, appropriately approved ex vivo human iris studies using sham-treated controls and prospectively defined sampling intervals. Laser characteristics would need to be fully described in a scientific validation study even where commercially sensitive implementation details are otherwise protected. Comparisons should account for baseline pigmentation, iris region, donor-level clustering, specimen handling, and possible confounding by age or previous medication.

These four domains can be operationalised without assuming any outcome. Organelle-level assays might include pigment quantification, electron microscopy, and validated optical measurements. Cellular readouts could comprise viability, cell-type-specific markers, apoptosis/necrosis indicators, oxidative-stress markers, and measured protein secretion. ECM studies could include collagen architecture, MMP activity rather than transcript alone, relevant TIMPs, and controlled measures of mechanical response where technically feasible. Sampling must permit acute and delayed responses to be distinguished, and analysis should predefine how results from paired eyes or multiple sectors are handled.

Table 3. Biological endpoints, candidate assays, and interpretation controls.

Biological domain	Candidate measurements	Proposed assay / method	Interpretive boundary
Pigment / melanosomes	Melanin content/distribution; melanosome ultrastructure; colour phenotype.	Melanin quantification; transmission electron microscopy; standardised colorimetry.	Reduced pigment does not establish melanocyte death.
Melanocyte viability	Cell-specific counts; membrane integrity; apoptosis-associated signals; melanogenesis.	SOX10/Melan-A immunolabeling; live/dead assays; cleaved caspase-3 or TUNEL with orthogonal controls.	TUNEL or a single apoptosis marker alone is not a quantitative viability assay.
Paracrine signalling	Melanocyte–fibroblast response; candidate SCF, HGF, FGF2 proteins.	Matched co-culture; RT-qPCR; ELISA or multiplex immunoassay of culture medium.	Candidate mediators are not established post-iris-laser pathways.
Macrophage–stromal crosstalk	Immune-cell phenotype and location; potential fibroblast-associated signalling.	Multiplex immunofluorescence; spatial phenotyping; controlled conditioned-medium assays.	Pigment phagocytosis alone does not demonstrate fibroblast modulation.
Extracellular matrix	Collagen organisation; active MMP/TIMP balance; fibronectin; mechanics.	Gelatin zymography (MMP-2/9); collagen imaging; immunohistochemistry.	Enzyme expression does not equal net matrix degradation or weakness.
Imaging correlation	Regional iris thickness, optical signal and pupillary response over time.	Registered high-resolution AS-OCT; repeatability and pupil-size controls.	OCT morphology is not a direct molecular or cell-viability assay.

FIGURE 3

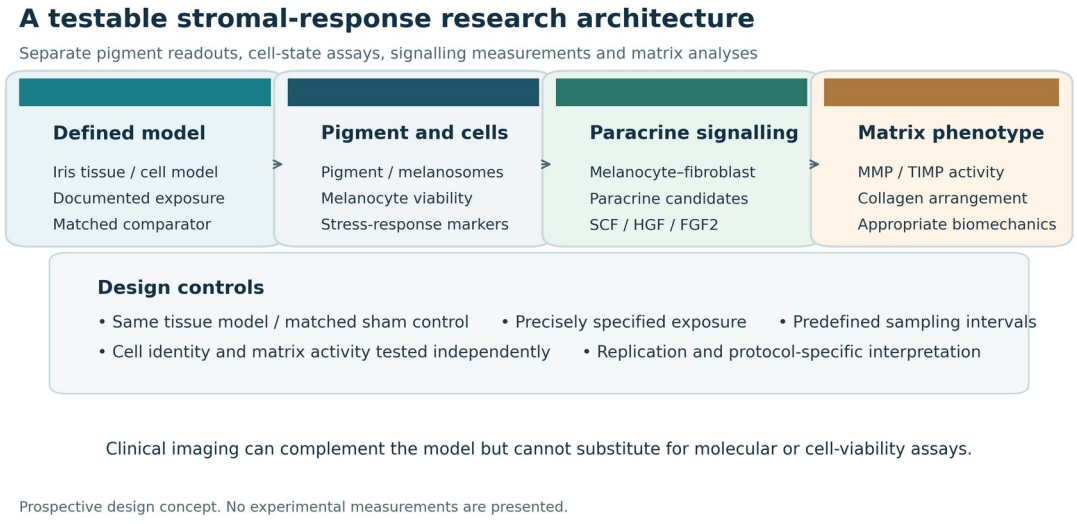

Figure 3. A staged validation strategy linking defined exposure and controls to cell-specific, molecular and matrix-level endpoints; proposed measurements rather than observed patient outcomes.

A complementary translational objective is to connect tissue-level biology with longitudinal in vivo imaging. High-resolution anterior segment optical coherence tomography (AS-OCT) can characterize regional iris thickness, stromal architecture, contour, and optical signal properties. Correlating these measures with matched experimental assays of melanocyte viability, collagen organization, and MMP/TIMP expression and activity could establish which imaging features, if any, reflect specific cellular or extracellular changes. Such correlations require controlled, paired validation: OCT signal intensity is influenced by pigmentation, acquisition conditions, and tissue optics and cannot directly measure enzyme activity, identify cell populations, or demonstrate collagen denaturation.

A further, secondary experimental phase could examine macrophage–stromal interactions. Human iris cell atlases identify immune-associated populations alongside melanocytic and non-melanocytic stromal cells [4,13]. In a defined laser-exposure model, spatial cell mapping, macrophage-specific phenotyping, and carefully controlled co-culture or conditioned-medium assays could test whether pigment handling is accompanied by macrophage-derived signals that alter fibroblast activity or matrix regulation. These potential paracrine interactions should be distinguished from pigment phagocytosis itself; their occurrence and direction after selective iris depigmentation have not been established. Serial clinical imaging may complement such experiments without replacing direct molecular or cell-specific measurements.

11. Relationship to pigment clearance, anterior-chamber response and temporal frameworks

The present question occupies a different tissue compartment from pigment-clearance kinetics and blood–aqueous barrier studies. Pigment clearance concerns the fate of released material; anterior-chamber response concerns cells, proteins, pressure, and outflow-related behaviour outside the irradiated stroma. A stromal study instead addresses the fate and functioning of cells and matrix at the exposure site. These biological levels may interact, but their measurement requirements are distinct. Related approaches, including L-SAFE and the companion preprints on P-CLEAR [19], blood–aqueous barrier dynamics [20], and Temporal Response Architecture [21], address complementary questions; none constitutes independent validation of stromal molecular mechanisms.

This distinction has practical scientific value: a visually successful colour modification and an apparently resolved anterior-chamber response are not equivalent to a direct demonstration of tissue-level recovery. Nor would evidence of transient molecular change by itself establish clinical harm. A coherent research programme should report each observation in the compartment where it was measured and reserve mechanistic attribution for evidence that tests it.

12. Uncertainties and limitations

The major limitation is the shortage of direct human iris studies examining molecular and matrix responses after well-characterised selective pigment-targeted exposure. Historical human iridotomy and iridoplasty pathology documents tissue effects but does not establish the responses of contemporary superficial stromal melanin modulation. The strongest iris-specific evidence in this synthesis establishes baseline tissue identity, regional protein distribution, melanocyte–neighbour-cell regulation, and modality-specific histopathological changes. It does not quantify a clinical post-laser molecular phenotype. The normal-tissue MMP/TIMP immunolocalisation study assessed seven postmortem eyes [12], while the 2025 iris single-cell analysis integrated only three donor irides [4]; these studies were not designed to measure treatment response. The cross-tissue studies differ substantially in cell lineage, pigmentation method, laser pulse characteristics, culture conditions, and functional endpoint. Consequently, proposed mediator pathways should not be presented as findings in treated human iris.

A second limitation concerns causality. Single-cell RNA sequencing describes cell populations and candidate gene programs, but is not a substitute for perturbation experiments. Immunoreactivity indicates protein localisation rather than matrix protease activity. Clinical photography provides an optical phenotype rather than a cell viability assay. Finally, a treatment-associated molecular change may represent adaptation, reversible stress, tissue injury, or benign variation; its significance requires independent structural and functional corroboration.

13. Conclusion

The irradiated iris stroma should be understood as a living multicellular tissue rather than a passive reservoir of melanin. Existing human iris studies establish fibroblast-dependent regulation of melanocyte function and an endogenous ECM-regulatory environment, while contemporary cell-resolved profiling provides a more precise map of relevant populations. Experiments in other laser-exposed tissues support the plausibility of delayed paracrine and matrix-related responses, but do not demonstrate them in the human iris. A meaningful next step is therefore to

distinguish melanosome modification, melanocyte fate, stromal signalling, and ECM behaviour through direct, controlled measurements. This compartment-resolved approach may provide a common experimental basis for comparing stromal biological responses across distinct pigment-targeted laser modalities, provided that exposure conditions and measurement methods are explicit. The central scientific advance is not to presume either structural preservation or damage; it is to specify what evidence would establish either conclusion.

Declarations

Author contributions. Mustafa Mete: conceptualisation, literature evaluation, translational synthesis, writing, critical revision and final approval.

Competing interests. Mustafa Mete is the developer of the Lumineyes™ method and is affiliated with MyLumineyes.

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Data availability. This review draws on the published literature cited below.

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