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## ***Discovery of a new regulator involved in skin aging: The Dynamic Interplay of Telocytes in Modulating WNT Signaling for Dermal-Epidermal Homeostasis***

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### **1. Introduction**

The skin is a complex organ composed of diverse cell types that must coordinate their behavior through intricate communication networks. Disruption of cell-cell communication among different skin cell populations can impair processes such as cell growth, development, and differentiation, ultimately inducing the onset of skin aging (1). The intercellular communication networks between fibroblast and keratinocyte represent a critical contributor to skin aging (2). Although studies have indicated that molecules such as laminin 511 and transmembrane collagens may be involved in mediating dermal-epidermal interactions (3, 4), the precise mechanisms and comprehensive communication pathways remain poorly understood. Given the essential role of intercellular communication in delaying skin aging and preserving tissue homeostasis, elucidating novel signaling pathways that regulate communication between the dermis and epidermis is pivotal for advancing our understanding of skin aging and developing effective anti-aging interventions.

We uncovered remarkable data on the functional plasticity of Telocytes (TCs), a recently identified mesenchymal cell type mediating epidermal-dermal communication during aging, known for their unique intercellular communication characteristics. The complex cellular junctional structures and the release of extracellular vesicles are important modes of intercellular communication of TCs (5, 6). In intestinal tissues, TCs help maintain epithelial structure and secrete essential WNT signals (7). Although WNT signaling typically supports skin stem cell self-renewal and differentiation, its dysregulation in aged skin leads to stem cell depletion and impaired regeneration. Diminished canonical WNT signaling is considered a hallmark of aging (8). It has been reported that TCs play an important role in regulating dermal cell activity and tissue structure formation through intercellular communication and paracrine signaling (9). The above findings indicate that TCs may intervene in the aging process through WNT signaling. However, their roles in skin aging remain poorly understood. To explore potential anti-aging

effects of TCs in skin, we performed histological examinations, single-cell RNA sequencing (scRNA-seq), and in vitro assays on human skin samples from individuals in different age groups. We aimed to clarify the relationship between TCs and aging, then elucidate underlying mechanisms in skin aging.

## 2. Materials and Methods

### Human Skin Samples

Human dorsal skin tissues were obtained from female donors and categorized into two age groups: young [YG] (n=2; aged <30 years) and old [OG] (n=2; aged >50 years). Tissues were used for cell isolation, scRNA-seq, paraffin embedding, and transmission electron microscopy. The study protocol was reviewed and approved by the local Ethics Committee.

### Immunofluorescence Staining (IF)

Paraffin-embedded tissue sections were deparaffinized and rehydrated. Antigen retrieval was performed by heating sections in citrate buffer. Non-specific binding was blocked with 5% bovine serum albumin (Boster, Cat# AR0004). Sections were incubated overnight at 4°C with primary antibodies against CD34 (Abcam, Cat# ab316277) and PDGFRA (Santa Cruz, Cat# sc-398206). After sections had been washed with phosphate-buffered saline (PBS), they were incubated with Alexa Fluor 488-conjugated (Proteintech, Cat# SA00013-2) and Alexa Fluor 594-conjugated (Proteintech, Cat# SA00013-3) secondary antibodies for 1 hour at room temperature. All antibodies were diluted 1:200. Nuclear staining was performed with DAPI (Beyotime, Cat# AR1177); antifade medium (Beyotime, Cat# P0126) was used for mounting. Slides were examined using a confocal microscope (Carl Zeiss, LSM900).

For TCs on fixed cell slides, fixative was aspirated and cells were washed three times with PBS. The IF procedure for fixed cell slides followed steps used for rehydrated paraffin sections.

### TEM

Human skin tissues were fixed with 2.5% glutaraldehyde in 0.2 M PBS (pH 7.4) at 4°C for 48 hours, then post-fixed with 1% osmium tetroxide at 4°C for 1–2 hours. Tissues were dehydrated through a graded acetone series (30%–100%) and embedded in Epon 812 resin. Ultrathin sections (50 nm) were cut, then stained with 1% uranyl acetate and lead citrate for 20 minutes. Sections were examined using a transmission electron microscope (Hitachi H-7650).

### Tissue Dissociation and Cell Purification for scRNA-seq

Fresh skin tissue was placed in a sterile culture dish containing 10 mL of 1× Dulbecco's PBS (Thermo Fisher, Cat# 14190144). A custom-formulated dissociation solution was prepared using collagenase type IV (Sigma-Aldrich, Cat# C5138), elastase (Sigma-Aldrich, Cat# E1250), and 10 µg/mL DNase I (Thermo Fisher, Cat# EN0523), dissolved in PBS supplemented with 5% fetal bovine serum (Thermo Fisher, Cat# SV30087.02). Skin tissue was digested at 37°C with 50 rpm shaking for approximately 40 minutes. The resulting cell suspension was sequentially filtered using 100-µm and 40-µm nylon cell strainers. Residual red blood cells were removed using 1× Red Blood Cell Lysis Solution (Thermo Fisher, Cat# 00-4333-57). Purified cell suspensions were processed for 10x Genomics library construction and 3' scRNA-seq via the Chromium™ Single Cell Controller (10x Genomics), which generated a water-in-oil emulsion.

### 10x Library Preparation and Sequencing

Beads containing unique molecular identifiers and cell-specific barcodes were loaded to near saturation, ensuring one bead per cell within each Gel Bead-in-Emulsion. Upon exposure to cell lysis buffer, polyadenylated RNA molecules hybridized to the barcoded beads. Beads were subsequently collected into a single tube for reverse transcription.

All downstream procedures followed the manufacturer's protocol for the Chromium Single Cell 3' v3.1 kit. Library quality and concentration were assessed by a High Sensitivity DNA Chip (Agilent) on a Bioanalyzer 2100 and the Qubit High Sensitivity DNA Assay (Thermo Fisher Scientific). Sequencing on a NovaSeq 6000 system (Illumina) used 2×150 bp paired-end reads.

### **scRNA-seq Data Analysis**

Read processing was conducted using the Cell Ranger v6.0.1 pipeline (default and recommended parameters). FASTQ files generated from Illumina sequencing were aligned to the rat/human genome (version mRatBN7.2/GRCh38.p13) using the STAR algorithm. Output was imported into the Seurat (v4.3.0) R toolkit for quality control and scRNA-seq. After quality control, a custom analysis pipeline was applied, incorporating Seurat commands, Harmony integration, doublet/erythrocyte elimination, principal component (dimensionality) ratio optimization, and t-distributed stochastic neighbor embedding (tSNE) reduction. The RDS object for each sample was saved without modifying count data.

### **Human Skin TC Isolation and Culture**

Human skin tissue samples were immediately transferred to sterile tubes containing DMEM/F12 medium (Gibco, Cat# 11330032) and rinsed with medium to remove residual blood. Tissues were minced into 1-mm<sup>3</sup> fragments and incubated at 37°C for 4 hours in PBS containing 1 mg/mL collagenase type II (Sigma-Aldrich). Resulting single-cell suspensions were filtered through 100-µm and 40-µm cell strainers (BD Falcon). Viable cells were resuspended in DMEM/F12 supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin (Sigma-Aldrich), then incubated at 37°C with 5% CO<sub>2</sub>. TCs were purified by differential adherence; TC-enriched non-adherent cells were collected after 4 hours and seeded in six-well culture plates.

### **Transwell Co-culture**

TCs were pre-cultured in the lower chamber for 8 hours to establish their microenvironment. Subsequently, immortalized human KCs (i.e., HaCaTs) and immortalized human FCs (HFFs) were seeded in the upper chamber of Transwell inserts (Corning) equipped with 0.4-µm pores to prevent direct cell contact while permitting diffusion of soluble factors. Co-cultures were maintained for 96 hours to allow extended interaction between TCs and HaCaTs/HFFs. After incubation, HaCaTs and HFFs were harvested for RNA extraction and subsequent qPCR analysis to evaluate TC factor-related changes in gene expression.

### **RNA Isolation and Quantitative PCR (qPCR)**

Total RNA was extracted from cells via TRIzol reagent (Invitrogen) and treated with gDNA Wiper Mix to eliminate genomic DNA before cDNA synthesis. qPCR was performed using SYBR Green PCR Master Mix (Vazyme Biotech Ltd.) on a LightCycler 96 (Roche). Relative gene expression was calculated by the 2<sup>-ΔΔCT</sup> method. Table 1 shows primer sequences. Each experiment was conducted in triplicate with ≥3 independent biological replicates.

**Table 1 Primers used for qPCR**

Gene	GeneBank accession no.	Sequence (5'→3')
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MYC	4609	AGGCATAAGGACTGGGAGT GTTGTGAAGGCAGCAGAAGC
TLE1	7088	GGGGACAAGAAGGCTACAG TCTGCTGATGGACTTGTCGC
TP53	7157	CCAGCCACCTGAAGTCCAAA AAACCCAAAATGGCAGGGGA
LAMC1	3915	GAGGCAAGATATGCCGTGA GTATCTGCCGTCCACTCG
ACTB	60	ACAGAGCCTCGCCTTGC AATCCTTCTGACCCATGCC
LAMB1	3912	GAAGACGGGAAGAAAGGGCA GCTCTGCACAGGGCTAAGAA
CTNNB1	1499	GCAGCAACAGTCTTACCTGG CATAGCAGCTCGTACCCCTCT
MAPK8	5599	TAACCCCCAGAGGAGTGAGGG AGACGCCAGCATCTTC

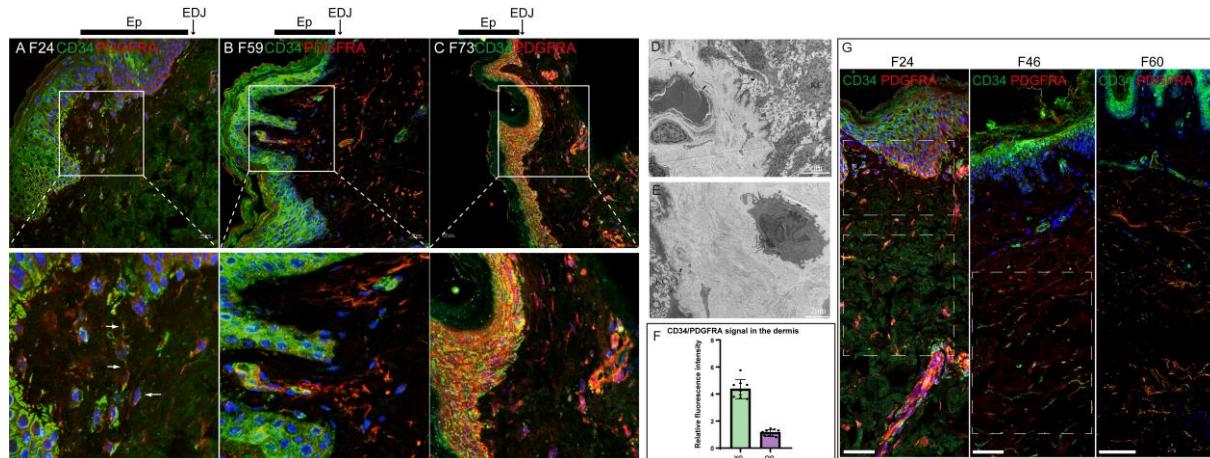
### Statistical analysis

All data are presented as mean±standard error of the mean. Statistical analyses and visualization were performed via GraphPad Prism 8. Differences between two groups were evaluated by unpaired Student's *t*-tests. *P*-values <0.05 were considered statistically significant.

### 3. Results

#### Young dermal TC (YTCs) exhibit distinct functional and morphological characteristics compared with older dermal TCs (OTCs)

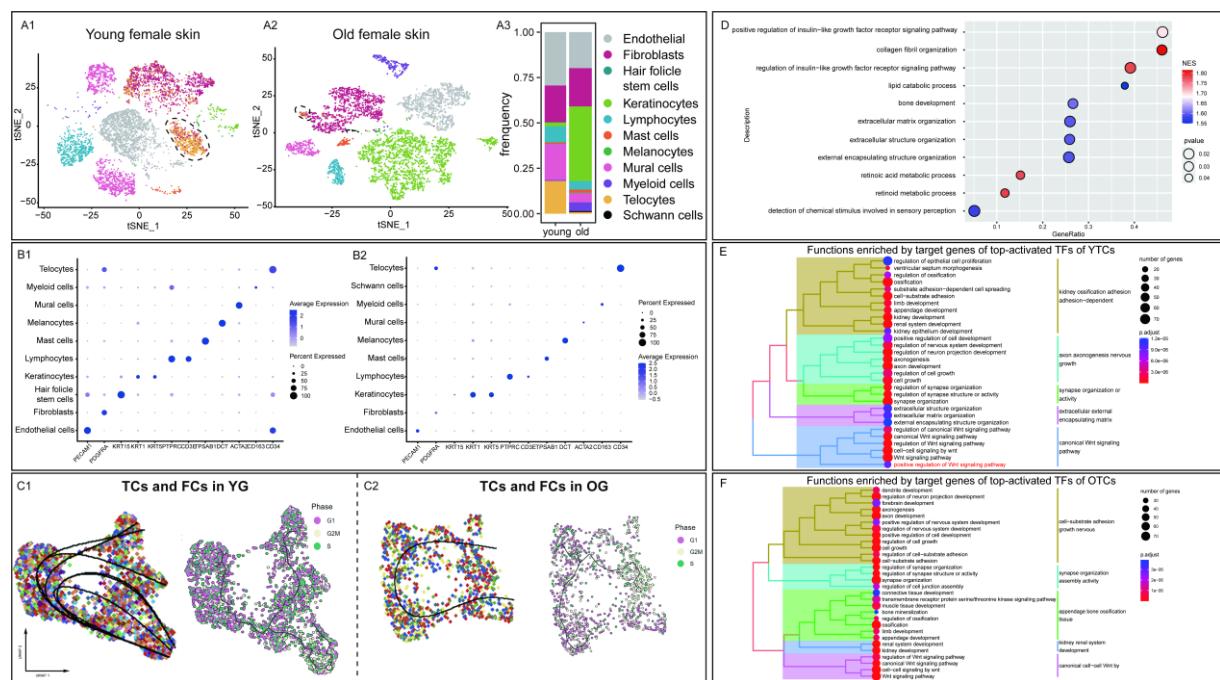
To investigate the distribution of TCs in the subepidermal region of skin from young and older female donors, IF analysis was performed on dorsal skin samples. In young skin, numerous subepidermal CD34+/PDGFRA+ TCs were evident (Figure 1A); in aged skin (Figure 1B, C), subepidermal CD34+/PDGFRA+ TCs were rare. TEM was used to validate these observations by comparing skin from 24-year-old and 73-year-old individuals. Young skin showed abundant TCs with elongated subepidermal projections (Figure 1D); aged skin rarely displayed TCs (Figure 1E). Quantitative analysis of samples from both groups, across various fields of view, confirmed this CD34/PDGFR expression trend (Figure 1F). Comparative analysis of TC distributions between age groups revealed prominent subepidermal telocyte-enriched areas (TEAs), characterized by TC clusters, in young skin. In middle-aged skin, TEAs were limited to deeper dermal layers; in older skin, these areas were greatly reduced (Figure 1G).



**Figure 1. YTCs exhibit distinct functional and morphological characteristics compared with OTCs.** (A) Subepidermal CD34/PDGFRα-stained YTCs (arrows) were detected, particularly in the papillary dermis. (B, C) OTCs were absent from YTC regions. (D) TEM revealed YTCs (arrows) beneath basal keratinocytes (KCs). (E) OTCs were absent; macrophages (MPs) were present. (F) Quantification of CD34/PDGFRα fluorescence in randomized dermal fields of view. (G) Distribution of TCs and TEAs (dashed box) across different age groups. Abbreviations: Ep, epidermis; EDJ, dermo-epidermal junction

#### scRNA-seq reveals distinct cellular compositions and functional differences between YTCs and OTCs

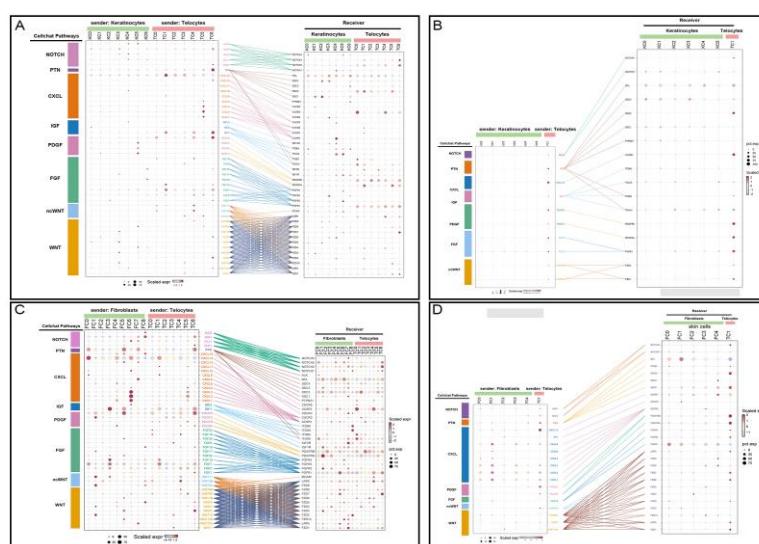
To comprehensively assess TC proportions and functions, we conducted scRNA-seq of skin samples from female donors in each group. tSNE reduction of sequencing data from the two age groups (Figure 2A1, A2) revealed distinct cell subpopulations defined by gene expression profiles (Figure 2B1, B2). Notably, young skin exhibited a substantial population of TCs; minimal TCs were present in aged skin (Figure 2A3). Given phenotypic similarities between TCs and fibroblasts (FCs), both expressing the mesenchymal marker PDGFRA (10, 11), we performed a comparative analysis focusing on cell cycle status and pseudotime trajectories. YTCs demonstrated greater proliferative capacity and more active differentiation trajectories. Two distinct subclusters—one for TCs and one for FCs—with high proportions of cells in the G2/M phase were identified as independent origins of divergent differentiation paths in young donors (Figure 2C1). Analysis of aged skin revealed only one trajectory originating from FCs, with no detectable lineage trace for TCs (Figure 2C2). Gene set enrichment analysis, based on differentially expressed genes between young and aged samples, indicated that YTCs contribute to growth factor regulation and collagen synthesis (Figure 2D). The Pyscenic algorithm was utilized to evaluate transcription factor (TF) activity in TCs across age groups. Analysis of the top 20 TF-regulated gene targets in each group revealed age-specific regulatory programs; YTCs displayed enhanced activity in WNT-related signaling pathways (Figure 2E, F).



**Figure 2. scRNA-seq reveals distinct cellular compositions and functional differences between YTCs and OTCs.** (A1–A3) Annotation and cell-type proportions from scRNA-seq data of YG and OG samples. (B1–B2) Identification of unique cell markers and average expression levels used for cell-type annotation. (C1–C2) Pseudotime trajectories and distribution of cell-cycle phases among TCs in YG and OG. (D) Functional enrichment analysis (Biological Process) of differentially expressed genes between YTCs and OTCs. (E, F) Functional enrichment of top 20 TF-regulated target genes in YTCs and OTCs.

### Cell communication analysis identifies age-associated differences in signaling characteristics of dermal TCs

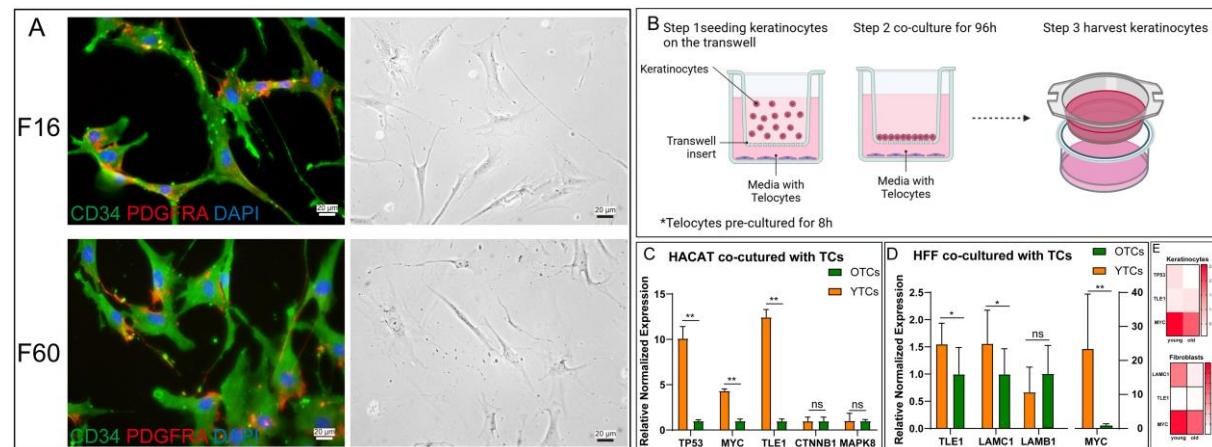
CellChat analysis revealed age-dependent variations in TC interactions with KCs. Although non-canonical WNT signaling and general connectivity pathways were both detected in young and aged samples, YTCs specifically engaged with KCs via canonical WNT signaling (Figure 3A). Conversely, canonical WNT signaling between OTCs and KCs was absent in aged individuals (Figure 3B). WNT signaling communication between TCs and FCs was observed in both age groups (Figure 3C, D).



**Figure 3. Cell communication analysis demonstrates age-associated differences in WNT between dermal TCs and KCs/FCs.** (A) Average expression levels and ligand–receptor interactions relevant to age-associated differences in TC–KC signaling in YG. (B) Corresponding analysis for TCs and KCs in OG. (C) Ligand–receptor interactions for TCs and FCs in YG. (D) Ligand–receptor interactions for TCs and FCs in OG.

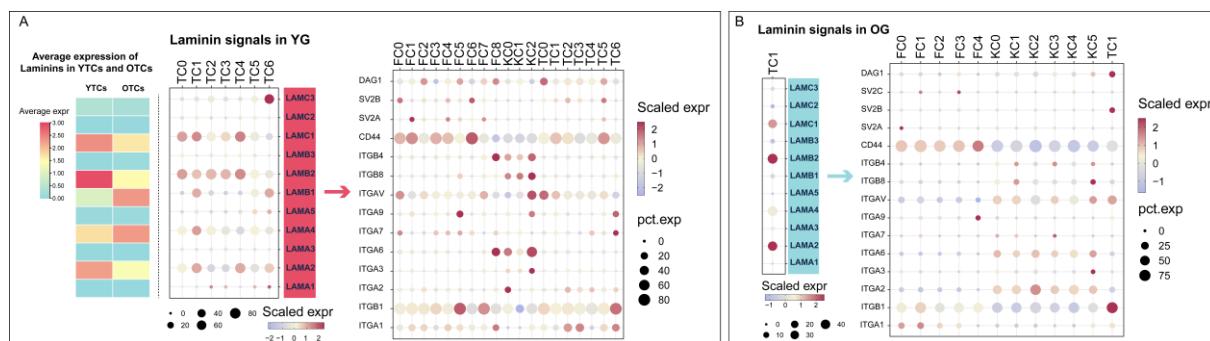
### YTCs promote a supportive microenvironment in co-culture with KCs and FCs

To explore YTC-regulated epidermal signaling, dermal TCs were isolated from donors aged 16 (F16) and 55 (F55). IF staining confirmed the CD34/PDGFR $\alpha$  phenotype; no notable morphological or immunophenotypic differences were evident between age groups (Figure 4A). HaCaTs and HFFs were co-cultured with dermal TCs from each age group using a Transwell system (Figure 4B). RNA extracted from HaCaT and HFF cells after 48 hours of co-culture revealed upregulation of several canonical WNT pathway downstream targets in response to TCs. MYC (c-Myc) and TLE1 (Transducin-like enhancer of split 1) expression levels increased in HaCaTs and HFFs (Figure 4C, D). These proteins are key WNT signaling effectors(12).



**Figure 4. YTCs promote a nurturing microenvironment in co-culture with KCs.** (A) Immunophenotype of TCs isolated from the skin of YG and OG donors, showing specific staining for CD34/PDGFR $\alpha$ . (B) Schematic of the Transwell co-culture system used for experiments involving YTCs, OTCs, and HaCaTs. (C) mRNA expression levels of TP53, MYC, and TLE1 in HaCaTs after 96 hours of co-culture with YTCs and OTCs. (D) mRNA expression levels of TLE1, LAMC1, and MYC in HFFs after 96 hours of co-culture with YTCs and OTCs. (E) Average expression of TC-regulated genes in KCs and FCs from YG and OG donors.

Given the essential role of the basement membrane (BM) in maintaining tissue integrity and the subepidermal localization of TCs, we used scRNA-seq to evaluate the expression of laminin, a major BM component, in YTCs and OTCs. Laminin, a non-collagenous protein that forms ECM networks(13), exhibited differential expression between age groups. Specifically, expression of laminin-511 subunits was age-dependent: LAMC1 expression was elevated in YTCs, whereas LAMB1 expression was higher in OTCs. These secreted laminin proteins were subsequently detected through integrin-mediated signaling in KCs, FCs, and TCs within each age group (Figure 5).



**Figure 5. Comparative expression profiles of laminin subunit and receptor genes.** (A) Intergroup comparison of laminin subunit gene expression, highlighting laminin signaling patterns in the YG mediated by YTCs. (B) Laminin signaling patterns in the OG mediated by OTCs.

Cells co-cultured with YTCs demonstrated elevated TP53 transcriptional activity in HaCaTs and increased LAMC1 expression in HFFs (Figure 4C, D). Furthermore, scRNA-seq data confirmed similar intergroup trends in TP53, LAMC1, and MYC expression in KCs and FCs, consistent with co-culture assay results. TLE1 expression did not significantly differ between age groups (Figure 4E).

#### 4. Discussion

This study utilized morphological approaches to examine previously uncharacterized distribution patterns of TCs in the context of female skin aging. With advancing age, TCs undergo considerable declines in quantity, quality, and spatial organization. These morphological findings were corroborated through scRNA-seq, which revealed age-related alterations in TC-associated cellular communication mechanisms. This highlights the potential importance of targeting TC-mediated communication as a therapeutic strategy to mitigate age-related skin degeneration.

In vitro assays confirmed that intercellular communication downstream of WNT pathway activation (e.g., TLE1, MYC) is modulated by TCs. The WNT signaling pathway, a conserved regulatory cascade, governs fundamental biological processes (e.g., embryonic development, cell differentiation, proliferation, and adult stem cell maintenance) (14). In aging skin, components of the WNT pathway exhibit abnormal expression patterns (15). For tissue homeostasis, the simultaneous upregulation of WNT signaling and inhibitory regulators such as TLE1 is essential to preserve structural and functional integrity (16). TLE1, in particular, plays a critical role in sustaining skin health and preventing age-related decline; its deficiency has been linked to impaired skin function (17). Likewise, MYC is regulated by canonical WNT signaling; it functions as a stabilizing factor in DNA replication and mitosis under appropriate microenvironmental conditions (18). In our study, YTCs induced KCs and FCs to upregulate MYC expression within an in vitro setting, indicating that YTCs play a pivotal role in establishing a supportive microenvironment via WNT signaling for aging regulation.

For the maintenance of dermal-epidermal homeostasis, upregulation of the WNT pathway was associated with increased TP53 expression in KCs and elevated LAMC1 expression in FCs, highlighting the role of intercellular communication in this process. Given MYC's global regulatory role in downstream gene expression, and the protective roles of TP53 in maintaining resistance to ultraviolet-induced DNA damage and laminins in the skin's anti-aging defense

mechanisms (19-21), our findings emphasize the complex regulatory network through which these factors mediate cellular responses to aging. Furthermore, TCs and FCs contribute to laminin secretion, which helps maintain the structural integrities of the BM and ECM, thus preserving skin homeostasis.

Given that WNT signaling benefits skin health, KCs and FCs engage in complex signaling involving hyaluronic acid (HA) and WNT pathways, with HA synthetase and the HA receptor CD44—key components of HA metabolism—directly interacting with MYC to promote skin health (22, 23). WNT signaling from TCs may mediate epidermal-dermal interactions by promoting cell proliferation and maintaining hydration, thus enhancing skin function. This highlights a potential therapeutic strategy for delaying skin aging and improving skin health.

Regarding methods to activate TCs, it has been found that mechanical stimuli can specifically activate TCs at particular sites on the skin surface (24). Accordingly, non-invasive devices targeting TC activation may offer broad applications for improving skin health. TC-based platforms may also facilitate the discovery of functional cosmetic ingredients. Thus, TCs are emerging as promising novel targets for skin anti-aging cosmetic strategies.

## 5. Conclusion

This study identified distinct TC phenotypes associated with the aging process, demonstrating that cutaneous intercellular communication alterations are key indicators of skin aging. In young skin, TCs help to maintain epithelial and dermal homeostasis primarily through WNT signaling, TP53 and ECM components such as collagen and elastin. Our findings highlight the critical role of TCs as a nexus between cellular communication and cutaneous vitality in the management of aging, with broader implications for overall health. They interact dynamically with FCs, stem cells, and immune cells to maintain skin function, counteract aging, and regulate dermal regeneration. These mechanisms underscore the broader principle that cellular communication is essential for holistic wellness, ensuring balanced and harmonized bodily functions. Future research should focus on TC rejuvenation and molecular interactions to advance anti-aging cosmetics and bridge skin-specific interventions with the holistic framework of overall well-being.

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