A New World of Anti-Aging Skincare Targeting the Face-Wrapping "Tensional Network": "Ring-Collagen"

-Paradigm Shift of Skin Analysis: From Visualizing Tangible to Intangible Targets-

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Background

1. "Wrapping force" is critical for youthful appearance

Youthful face — Skin physically "wraps" understructures. Subcutis, Skin. "Wrapping force" Retain morphology.

Facial aging process — Loss of "wrapping force". Loose. Lost. Fundamental cause of facial aging. Gravity causes sagging of skin / understructures. Gravity. Sagging (aged face). Lost.

However "wrapping" system is still unclear. Ezure 2009 Skin Res Technol

2. Wrapping force (physical dynamics) is inaccessible by current technology

<Progress of skin visualization>
Tangible world: Structure (cells, internal organs). 2D (1600), 3D (2016), 4D (2020). Ezure IFSCC2016. Movement. Ezure, IFSCC2020.
Intangible world: Physical dynamics. Need a paradigm shift. (Year) Now.

Objectives

1. To visualize 4D skin physical dynamics
2. To clarify how skin wraps the face to retain morphology
3. To develop impactful anti-aging solution

Methods

Skin specimens: 137 surplus facial skin (age: 0-103); 30 abdominal female skin (age: 22-73)

Human testing: 30 female volunteers (age: 30-40s): skin analysis; 6 female volunteers (40s): efficacy test. Sagging: photograph-based grading [2]. Skin physical properties Cutometer 580®

X-ray micro CT: X-ray CT: Xradia; Zeiss (Oberkochen) (50 kV, 80 µA). AI: Dragonfly (Object Research Systems). High-speed autostereoscopy: our new program. Viewing of autostereoscopy: SR display (SONY)

Organ and cell culture: Fibroblasts (Lonza) / skin: DMEM with 10% FBS. Human outer root sheath (ORS) cells: established from human skin, cultured in K-SFM (Gibco)

Result 1. Visualization of intangible 4D skin physical properties in real-space: "skin-mechanics reality"

1. Visualization of intangible 4D skin physical properties

1) 4D skin dynamics analysis — Observation scheme: Deformation / recovery. X-ray micro CT. 3D CT images: Twist. Structure identification. AI-based auto-identification.

2) 4D skin physical property reconstruction — Setting the observation points: High density meshes. 20,000 < points / mesh. 1,000,000 < points / skin. Tracking the observation points: Twist. 4D reconstructed physical properties.

2. Real-space reconstruction of 4D physical dynamics

Scheme of autostereoscopy: 1. Tracking eye position. Detector. Display. 2. Projecting & moving images. Our new high-speed autostereoscopy program enables real-time viewing.

Not a toy, but enabling actual research: Complex data understanding, Operate other devices, Discussion.

4D image moves according to position of eyes in real space. "Skin-mechanics reality"

This illustrates the spatially reconstructed 4D skin mechanics image in real space

3. "Skin-mechanics reality" provides unprecedented information about skin physical properties

Ultra-high resolution 4D skin physical information. Tension view. Composed of millions of area's information (cones): 1,000,000 areas (shown by cones). Cones. Anatomy of tangible and intangible skin targets: Hair follicles, Sebaceous gland, Arrector pili, Sweat gland, Cut off, Dermis. Cones: direction and strength of tension.

Real-time view of skin physical property: Arrow: direction and strength of tension. Visualizing skin property even without structure: Arrow: direction and strength of tension. Real-time sorting / viewing physical property by figure: Sweat glands, Sebaceous glands, Hair muscles, Hair follicles.

These are not CG images (actual 4D image data). Tension: determined as the difference between the initial and subsequent states of each point.

Result 2. "Ring-collagen" produces a tensional network to form wrapping force of the face, to retain facial morphology

1. Facial skin contains ring-shaped high-tension areas in the deep dermal layer

1) Tension analysis system — Dissection. Original size. Self-contraction. Analyze tension: Expand, Contract. Original size.

2) High tension areas exist at the deeper dermis — Skin tension is uneven. High tension area. Dermis. Tension: high.

3) Distribution of high tension sites in dermis — High tension area. % of high tension area vs Depth (µm).

4) High tension area of deep dermis forms ring-shapes — Ring-shaped high tension area (red). Dermis.

5) Ring-shaped high tension area exerts center-directed tension — Tension direction. (magnified).

6) Center-directed high tension area produces skin tension — 1. Ring-shaped high tension areas. Dermis. 2. Center-directed tension. 3. Total skin tension.

2. Ring-shaped collagen, called "ring-collagen", surrounding proteoglycans produces high tension

1) Relationship between tension and structures — Total dermis. Dermis. Hair muscle, Sweat gland, Sebaceous gland. High tension area (red): few structures. Low tension area: fine hair + unclear structure. Lower dermis. Low tension area.

2) Low tension area contains fine hair surrounded by proteoglycans (PGs) — Low tension area. Fine hair. PGs: Versican, Periostin. Fine hair.

3) High tension area: ring-shaped collagen — Top view.

4) PG layer contributes less to skin tension — Relative tension (%): Ring-collagen, PG layer (N=3, **: P<0.01). Facial skin tension-producing system: Fine hair, Center-directed tension, Dermis, PG layer, Skin tension. "Ring-collagen"

3. Ring-collagen produces a tensional network, which creates "wrapping force" to maintain facial morphology

1) Collagen content is low in facial skin — Body: Fine hair, Collagen: high. Face: Fine hairs, Collagen: low. Collagen content: Body, Face (N=5, ***: P<0.001). How to maintain facial shape with low collagen? Only 50%?

2) Ring-collagen fibers pull each other — Tensioned. PGs, Fibers, Relaxed, Mutually pulling. Pressed: Tension (white arrow). Sum of tension (red arrow): Tensional network.

3) Ring-collagens produce tensional network.

1. Collagen fiber: Relaxed, Expanded (in the body), Fiber-derived contraction force. 2. Ring-collagen: Mutually pulling, Tension, Center-directed tension. 3. Tensional network: Skin tension. 4. In the face: Fixed, Ligaments / muscles, Wrapping force.

1,2. Contraction of collagen fibers in ring-collagen generates a center-directed tension, 3. and the sum of them create a tensional network, 4. which in turn interacts with ligaments/ muscles to form a large "wrapping force" that maintains facial morphology.

Result 3. "Ring-collagen" decreases with aging, leading to aged appearance

1. Ring-collagen deteriorates with aging by loss of PG layer

1) Ring-collagen becomes sparse as PG layer is lost with aging — Young: Ring: clear, PG layer: thick, PGs (Versican), Collagen: dense. Old: Ring: unclear, PG layer: lost, PGs (Versican), Collagen: sparse. Ring-collagen decreases with aging: Diameter (µm) Young, Old (**).

2) High tension area is lost with aging — Young: Dermis, Abundant. Old: Dermis, Lost. Loss of PG layer deteriorates ring-collagen with aging: Young: Ring-collagen, PG layer, Fibers: dense. Old: Lost ring-collagen, Lost PG layer, Fibers: sparse.

2. Establishment of non-invasive ring-collagen evaluation system

1) Ring size is related to thickness of fine hair — Hair: thick, PG layer: large. Hair: thin, PG layer: small. Ring-collagen diameter (µm) vs Fine hair diameter (µm): Y = 5.34 X + 102.48, R = 0.73 (p<0.001). Fine hair: Thickness / density, Can predict, Ring-collagen: Thickness / density.

2) Grading criteria of fine hairs to predict ring-collagen condition — 0, 1, 2, 3, 4, 5. 0: None. 1: Thin fine hairs are sparsely visible. 2: Medium fine hairs are sparsely visible. 3: Medium fine hairs are visible. 4: Thick fine hairs are sparsely visible. 5: Thick fine hairs are densely visible.

3. Loss of ring-collagen decreases skin elasticity and induces sagging

30 female cheeks

	Ring-collagen condition	
	R	P-value
Skin elasticity (Ur/Ue)	0.406	<0.05
Sagging severity	-0.398	< 0.05

Loss of ring-collagen with aging decreases wrapping force and results in aged face — Young: "Ring-collagen", Retain morphology, "Wrapping force". Old: Sagging, Lose ring-collagen, Lose PG layer (core of ring-collagen), Lose wrapping force, Sagging (aged face).

Result 4. Novel anti-aging skincare solution; "Environmental transplantation"

1. Ring-collagen is a skin tension organizer; sensing/remodeling itself to adapt to physical skin condition

1) Identification of ring-collagen inducer — Microdissection of facial skin. Fine hair, Ring-collagen, PG layer, Hair cell (ORS), Fibroblast. Compare gene expression: Secretory factors (ORS > fibroblasts). Microarray, RNA-seq: 44, 36, 280. Candidate factors.

2) Wnt16 induces PGs expression in fibroblasts — Versican. mRNA abundance: Cont., Wnt16. ORS, Wnt16, Fibroblast, Produce PGs. Wnt16: 1µl/mL for 2 days (N=3, **: P<0.01). Periostin also increased significantly.

3) Wnt16 decreases with aging in fine hair — Young, Old. WNT16. Wnt16 grading: Young, Old (N=5, Old; N=6, **: P<0.01).

4) Physical burden regenerates ring-collagen via Wnt16 and PGs induction — Wnt16, PGs (Versican). Control, Extended. 30 % extension. Skin culture: 7 days. Ring-collagen: Diameter (% of cont.), Cont. Tensioned (N=3, **: P<0.01). Induced.

Ring-collagen: skin tension organizer (sensor / regulator) — 1. Physical burden. 2. Remodeling ring-collagen. 3. Skin tension reconstruction. Increase ring size and collagen density. i) Physical burden. ii) Wnt16 (ring-collagen inducer). iii) Produce PGs (core of ring-collagen). PG layer, ORS, Fibroblast.

2. "Environmental transplantation" rejuvenates the face

1) Transplantation of physical environment — Young: Physical burden: high, Loading physical burden of young skin. Old: Physical burden: lost (Loss of volume (bone, fat and muscle), Loss of activity (facial expression)). Ramirez, 2001, Facial Plast. Surg.

【Human test】
2) Physical burden improves wrapping force and aged face — Female volunteers (40s, N=6). 30% extension of skin once a day for 28 days. Before, After. Sagging. Marionette lines: marker of sagging. Lower cheek (as representative). Sagging (Grading): Improvement (%) vs Days (0, 7, 14, 21, 28). Wrapping force (Refer to res.3.3): Improvement (%) Before, After.

Solution: "Environmental transplantation" — 1. Transplant physical environment. 2. Regenerate ring-collagen. 3. Restores wrapping force. 4. Facial rejuvenation. Young, Old. i) Physical stimulation. ii) Wnt16 (ring-collagen inducer). iii) Produces PGs (core of ring-collagen). Lost ring-collagen, Ring-collagen, Fibroblast.

Conclusion

Ⅰ. Technology: "Skin-mechanics reality". Paradigm shift of skin analysis.

Ⅱ. Discovery: 1. Facial morphology retaining system. "Ring-collagen". "Wrapping force". 2. Skin tension organizer: Sensing signal (via fine hair), Wnt16 (Inducer), Remodeling. 3. Facial aging mechanism: Loss of ring-collagen, Loss of wrapping force, Sagging (aged face).

Ⅲ. Solution: "Environmental transplantation". Young, Old. Loading physical burden of young skin.

A new world of skincare.

Ⅰ. Technology: We visualized 4D physical dynamics, "Skin-mechanics reality", providing a paradigm shift of skin analysis from tangible to intangible world.

Ⅱ. Discovery: 1. We identified a facial skin-specific tensional network generated by "ring-collagen": It physically wraps the face to retain facial morphology. 2. Ring-collagen is a skin tension organizer. It senses the skin's physical environment via fine hair (Wnt16-PGs system), and remodels itself to adapt to the environment. 3. Aging decreases the skin's physical burden, which decreases PGs (core of ring-collagen). This deteriorates ring-collagen, decreasing the wrapping force, which leads to sagging.

Ⅲ. Solution: We developed "environmental transplantation", loading the physical burden of young skin. This regenerates ring-collagen, resulting in facial rejuvenation.

Thus, our technology, discovery and solution open up a new world of skincare.