Topical Use of Growth Factors & Stem Cells in Skin Care

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Skin Aging & Wound Healing

• Exposure to UV radiation causes damage that accelerates chronological aging and exacerbates skin injury, resulting in photodamage
• Correlation exists between photodamage and wound healing

Growth Factors

• Regulatory proteins that mediate signaling pathways between and within cells
• Essential for wound healing
Growth Factors

- Cytokines: proteins produced by variety of cell types
- Function to regulate cell growth, development and activation, mediation of immune response
- Tissue repair result of interaction of many cytokines and growth factors working to re-establish balanced homeostatic environment

Phases of Wound Healing

- Wound
- Hemostasis
- Inflammation
- Granulation
- Remodeling

Hemostasis

- Key growth factors
  - TNF α (tumor necrosis factor)
  - Inflammatory interleukins
- Activity
  - Neutrophils, platelets, and plasma proteins infiltrate the wound and initiate vasoconstriction
  - Platelets release clotting factors to initiate coagulation
  - Platelets release cytokine and growth factors that attract neutrophils, macrophages, and other cells necessary for cutaneous healing
**Inflammation**

- Key growth factors
  - TGF-β
  - TNF-α
  - IL-1, IL-6, IL-8, IL-10
- Activity
  - Neutrophils initiate phagocytosis and attract macrophages
  - Macrophages continue phagocytosis and release additional growth factors and cytokines which attract fibroblasts to the wound, promote angiogenesis, and stimulate keratinocyte growth

**Granulation**

- Key growth factors
  - TGF-β
  - PDGF
  - VEGF
  - HGF
  - NGF
  - IGF
  - IL-8
- Activity
  - Fibroblasts synthesize collagen
  - New collagen fibers begin to form matrix or scaffold for additional fibroblast attachment
Remodeling

- Key growth factors
  - TGF-β
  - FGF-2
  - TIMPs
  - MMPs

Remodeling

- Activity
  - Collagen fibers are remodeled, or cross-linked, into an organized matrix
  - Additional collagen fibers attach to the matrix and assemble into new tissue
  - Wound contraction and tissue strengthening occur

Growth Factors/Cytokines in the Skin

- Fibroblast growth factor (FGF)
- Hepatocyte growth factor (HGF)
- Platelet-derived growth factor (PDGF)
- Insulin-like growth factor (IGF)
- Transforming growth factor (TGF)
- Tissue inhibitor of metalloproteinases (TIMP)
- Vascular endothelial growth factor (VEGF)
- Placenta growth factor (PGF)
- Bone morphogenetic factor (BMP-7)
- Interleukins
- Leptin
- Colony-stimulating factors
**Fibroblast Growth Factors**
- bFGF, FGF-2, FGF-4, FGF-6, KGF, FGF-7, FGF-9
- Angiogenic
- Fibroblast mitogen

**Hepatocyte Growth Factor**
- HGF
- Strong mitogenic activities
- Three-dimensional tissue regeneration and wound healing

**PDGF**
- Platelet derived growth factor
- Chemotactic for fibroblasts and macrophages
- Mitogenic for fibroblasts, smooth muscle, and endothelial cells

**Insulin-Like Growth Factor**
- IGF-1, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-6
- Endothelial cell mitogen
- Fibroblast mitogen

**Transforming Growth Factor (TGF)**
- Regulates new blood vessel formation (angiogenesis)
- Chemotactic for fibroblasts, keratinocytes, and macrophages
- Mitogenic for fibroblasts and smooth muscles cells
- Inhibits endothelial cells, keratinocytes, and lymphocytes
- Regulates matrix proteins including collagen, proteoglycans, fibronectin, and matrix-degrading proteins

**Tissue Inhibitor of Metalloproteinases**
- TIMP-1, MPI-1, TIMP-2, MPI-2
- Prevent enzymatic degradation of collagen and hyaluronic acid
**VEGF**

- Vascular Endothelial Growth Factor
- Mediates angiogenesis
- Chemotactic for endothelial cells
- Mitogenic for endothelial cells and keratinocytes

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**Placenta Growth Factor**

- PLGF
- Promote endothelial cell growth

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**Bone Morphogenic Protein**

- BMP-7
- Promote development of nerve cells in developing tissue
Interleukins

- IL-1α & β: early activators of growth factor expression in macrophages, keratinocytes, and fibroblasts
- IL-2: enhance epithelial wound healing
- IL-6: mediator of acute phase response to wound; synergistic effect with IL-1
- IL-10: inhibits pro-inflammatory cytokines to reduce inflammation; prevents scar formation

Interleukins

- IL-3, IL-4: stimulate production of IL-6
- IL-3, IL-4, IL-5: leukocytes maturation and degranulation during inflammatory phase
- IL-7, IL-8, IL-15: leukocyte activation and proliferation during inflammatory phase

Leptin

- Epidermal keratinocyte proliferation during wound healing
**Colony Stimulating Factors**

- GCSF, GM-CSF, M-CSF
- Stimulate development of neutrophils and macrophages

**Growth Factors & Cytokines**

- Provide communication between immune system, keratinocytes, and fibroblasts through process of wound healing, skin repair, and regeneration
- During wound healing, growth factors and cytokines work to improve extracellular matrix
- Growth factors used individually unlikely to produce results

**Topical Human Growth Factors**

- Very large molecular weight molecules
- Questionable delivery across stratum corneum
- Capable of increasing protein and collagen production
- May require presence of other regulatory proteins
Products Containing Growth Factor

• TNS Recovery Complex, SkinMedica
  – Nutrient solution neonatal fibroblasts
• Natura Bisse
  – 4% skin growth factor placental extract
• Re Vive, Chiron Bays Brown Labs
  – Recombinant EGF
• Jan Marini Transformation Line
  – Recombinant TGF-beta-1

TNS Recovery Complex with NouriCel-MD to Reverse Photodamage

• 14 patients with Class II photodamage
• Application of TNS Recovery Complex with NouriCel-MD BID x 60 days
• Pre and Post evaluation
  – Clinical grading of photodamage
  – Optical profilometry
  – 3 mm punch biopsy
  – Patient questionnaire


Results

• 11 of 14 patients showed clinical improvement in at least one facial area
• Periorbital wrinkles significant improvement by optical profilometry

TNS Recovery Complex with NouriCel MD

Split Face Study TNS vs. Placebo
- TNS Recovery Complex is associated with improvement compared to placebo
- Improvement in skin texture and decrease in appearance of wrinkles
- Subjects consistently noticed an improvement in the appearance of their wrinkles after using TNS Recovery Complex
- Optical profilometry demonstrated a reduction in skin roughness and wrinkles
- These data also suggest that there is a continued effect 3 month post application

Growth Factor Results

Human Growth Factor Skin Cream Study
- 18 patients Fitzpatrick II or greater photodamage
- Double-blind
- Applied Bio-Restorative skin cream twice daily for 60 days
- Significant improvement seen in facial wrinkle parameters via 3-dimensional surface mapping technique

Risks of Non-Autologous Human Growth Factor Use

- Potential for topically applied growth factors to stimulate development of cancer cells
- Unlikely topically applied growth factors would affect tumor growth as molecules are too large to be absorbed

Synthetic Growth Factors

<table>
<thead>
<tr>
<th>INCI Name</th>
<th>Growth Factor</th>
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<tbody>
<tr>
<td>Human Oligopeptide-1</td>
<td>Epidermal growth factor</td>
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<td>Insulin-like growth factor</td>
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<td>Nerve growth factor</td>
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<tr>
<td>Human Oligopeptide-20</td>
<td>Tissue inhibitor of metalloproteinases</td>
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Kinetin

- Plant-derived growth hormone
- Regulates cellular differentiation by endocrine pathway with unknown mechanism
- Retards leaf yellowing and senescence
- Slows down fruit ripening and degeneration
Kinetin

- Studies on human fibroblasts in vitro demonstrate that kinetin may have the ability to delay onset of age-related changes and decrease severity
  - Alteration in cell size and shape
  - Growth rates
  - Macromolecular synthesis

Kinetin Mechanism of Action

- Inhibitor of reactive oxygen species (ROS) formation
- ROS scavenger
- Mimics superoxide dismutase (SOD) activity
- Prevent oxidation of unsaturated fatty acids and inhibit DNA oxidation
- Inhibits oxidation and glycation/glycoxidation of proteins

Kinetin Clinical Studies

- Anti-aging effects of topical kinetin 0.03% in combination with niacinamide 4% versus niacinamide alone in Asian skin
- Combination of niacinamide and kinetin showed reduced number of hyperpigmented spots and blotchiness as well as increased stratum corneum hydration

Use of Stem Cells in Skin Care & Rejuvenation

• Adipose tissue represents abundant, reliable source of adult stem cells
• Ability to differentiate along osteogenic, myogenic, neurogenic and hematopoietic pathways
• Adipose stem cells are known to participate in neovascularization and healing process of skin, both directly and indirectly

Adipose-Derived Stem Cells & Wound Healing

• Participate in angiogenesis and wound healing
• ASCs derived from human adipose tissue secrete:
  – VEGF (vascular endothelial growth factor)
  – HGF (hepatocyte growth factor)
  – TGF-β (transforming growth factor)

ASCs & Wound Healing

• Amount of VEGF secretion increases 5-fold under hypoxic conditions
• Capable of high proliferative rates, enhancing repair with increased release of angiogenic factors (VEGF and FGF)
ADSCs & Wound Healing

- ADSCs advantageous over utilizing single growth factor
- Stem cells interact with environment and modulate activity to release multiple factors
- Can serve as source for producing skin substitutes
- Multiple studies show that ADSCs can differentiate to directly participate in structural wound repair via differentiation into epidermal keratinocytes, endothelial cells, and pericytes

Stem Cell-Based Theory for Wound Healing

- Stem cells applied to wounds contribute to healing by differentiating into cells that form building blocks for tissue renewal (keratinocytes) and/or by modulating wound repair by release of growth factors (FGF and VEGF) via paracrine signaling
- Growth factors thought to play role in responses to cutaneous injury, including angiogenesis, fibroproliferation, and inflammatory response


- Currently conducting studies for the topical use of ADSCs post laser resurfacing
- Evaluating pain levels, inflammation, and healing time when compared with control
- Preliminary results very promising