Wound Healing with Beta-Adrenergic Receptor Antagonists

Robert S. Kirsner, M.D., PhD
Vice Chairman, Professor and Stiefel Laboratories Chair
Department of Dermatology and Cutaneous Surgery
University of Miami Miller School of Medicine
Miami, Florida
History

- 43 year old women after childbirth January 14, 1994, developed postpartum cardiomyopathy requiring heart transplant in 1994
Postpartum cardiomyopathy

Type of dilated cardiomyopathy

Rare: 1 in every 1,300 - 4,000 deliveries

During last month of pregnancy or within 5 months of delivery

Cause unknown
Physical Exam April 2010
July-October 2010

Started on Regranex gel (recombinant human platelet-derived growth factor)

Timolol ophthalmologic 0.5% solution added

In 8 weeks, her wound showed rapid rate of repiethelialization
# Mediators of re-epithelialization

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Receptor</th>
<th>Type of receptor</th>
<th>Signalling proteins</th>
<th>Role in re-epithelialization</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGF</td>
<td>MET</td>
<td>Receptor tyrosine kinase</td>
<td>Unknown, possibly ERK1 and ERK2, AKT, GAB1, PAK1 and/or PAK2</td>
<td>Stimulation of keratinocyte migration and probably proliferation</td>
<td>43</td>
</tr>
<tr>
<td>FGF7, FGF10 and FGF22</td>
<td>FGFR2-IIIb, possibly FGFR1-IIIb</td>
<td>Receptor tyrosine kinase</td>
<td>Unknown, possibly ERK1, ERK2, AKT and/or STAT3</td>
<td>Stimulation of keratinocyte proliferation and migration</td>
<td>44-46</td>
</tr>
<tr>
<td>Heparin-binding EGF and other EGF-family members</td>
<td>EGFR (also known as ERBB1), possibly ERBB2, ERBB3 and/or ERBB4</td>
<td>Receptor tyrosine kinase</td>
<td>Unknown, possibly ERK1 and ERK2, AKT and/or STAT3</td>
<td>Stimulation of keratinocyte proliferation and migration</td>
<td>30, 47</td>
</tr>
<tr>
<td>TGF-β</td>
<td>TGF-βreceptor I and TGF-βreceptor II</td>
<td>Receptor serine/threonine kinase</td>
<td>SMAD3 and others, including SMAD2 and MAPK</td>
<td>Inhibition of keratinocyte proliferation and survival</td>
<td>30, 51, 52</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>M3 receptor</td>
<td>G-protein-coupled receptor</td>
<td>Ca(^{2+})-dependent guanylyl cyclase, cyclic GMP and PKG, leading to inhibition of RHO</td>
<td>Inhibition of keratinocyte migration</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>M4 receptor</td>
<td>G-protein-coupled receptor</td>
<td>Adenylly cyclase, cyclic AMP and PKA</td>
<td>Stimulation of keratinocyte</td>
<td>54</td>
</tr>
<tr>
<td>Catecholamines, including adrenaline</td>
<td>β₂-Adrenoreceptor</td>
<td>G-protein-coupled receptor</td>
<td>Activation of phosphatase PP2A, resulting in dephosphorylation and inhibition of ERK1 and ERK2</td>
<td>Inhibition of keratinocyte migration</td>
<td>55</td>
</tr>
</tbody>
</table>

EGF, epidermal growth factor; EGFR, EGF receptor; ERK, extracellular-signal-regulated kinase; FGF, fibroblast growth factor; FGFR1-IIIb, IIb isoform of FGF receptor 1; GAB1, growth-factor-receptor-bound protein 2 (GRB2)-associated binding protein 1; HGF, hepatocyte growth factor; M3, muscarinic receptor subtype 3; PAK, p21-activated kinase; PKA, cyclic-AMP dependent protein kinase; PKG, cyclic-GMP-dependent protein kinase; PPAR, peroxisome-proliferator-activated receptor; SMAD3, SMAD-family member 3; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β. *PPAR-β ligands might be fatty acids.
Adrenergic Receptors

- **α- 1**
  - Vasoconstriction
  - ↑Peripheral Resistance
  - ↑BP
  - Mydriasis
  - ↑sphincter closure

- **α- 2**
  - Inhibit NE release
  - Inhibit insulin release

- **β- 1**
  - Tachycardia,
  - ↑lipolysis,
  - ↑myocardial contractility,
  - ↑renin

- **β- 2**
  - Vasodilation, bronchodilation
  - ↑muscle and liver glycogenolysis,
  - ↑glucagon, relax uterine smooth muscle
β2 Antagonists and Re-epithelialization

• Two proposed mechanisms
  – β2 antagonists enhance ability of keratinocytes to respond to electrical fields created by wounds
  – Via PP2A (protein phosphatase 2A) and ERK (extracellular signal-regulated kinase), β2 antagonists increase keratinocyte proliferation and migration
Beta-2 adrenergic receptor signaling
β-AR antagonists enhance skin wound re-epithelialization

Pullar C E et al. J. Biol. Chem. 2006;281:21225-21235
Burn patients

Double-blind randomized clinical trial; a total of 79 burn patient; 37 pts in propranolol group vs 42 pts in placebo group

Conclusion

Topical Beta-blockers may be an easy, effective, and inexpensive way to speed epithelialization in chronic wounds. Further, studies are needed.
References