ESPEN Congress Prague 2007

Nutrition and Wound healing

Wound healing – basic principles

Lubos Sobotka
Wound healing – basic principles

Lubos Sobotka
Department of Metabolic Care and Gerontology
Medical Faculty – Charles University
Hradec Králové
Czech Republic
Learning objectives

• To know basic principles of wound healing
• To understand the difference between regeneration and adult wound healing
• To be aware of effect of stress and inflammation on wound healing process
• To be informed about an effect of chronic disease on wound healing
• To know that undernutrition affects wound healing
Basic principles
Wound healing

foetal
- Regeneration - scarless

late-foetal & adult
- Contraction
- Scar formation
Regeneration
Scarless healing

Scar formation

Yannas I.V. 2005
# Adult and fetal wound healing

<table>
<thead>
<tr>
<th>Wound Healing Characteristics</th>
<th>Adult</th>
<th>Fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Cell Proliferation</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Speed to closure</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Scab</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Oxygen tension</td>
<td>Greater</td>
<td>Lesser</td>
</tr>
<tr>
<td>Fluid environment</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Sterile environment</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Skin temperature</td>
<td>Cooler</td>
<td>Warmer</td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>Greater</td>
<td>Lesser</td>
</tr>
<tr>
<td>Matrix deposition</td>
<td>Slower, disorganized</td>
<td>Faster, organized</td>
</tr>
<tr>
<td>TGFβ &amp; bFGF</td>
<td>Greater</td>
<td>Lesser</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Greater</td>
<td>Lesser</td>
</tr>
<tr>
<td>Epithelialization</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Keratinization</td>
<td>Present</td>
<td>Immature</td>
</tr>
</tbody>
</table>

Adzick NS, Lorenz HP 1994
Inflammation - central role in adult wound healing - scar formation

Hunt TK, J Trauma 1990
Scar formation

Adzick NS, Lorenz HP 1994
Adult wound healing

- Coagulation
- Inflammation
- Tissue formation
- Remodeling
Coagulation

Singer et al. NEJM 1999
Coagulation

- **Platelets** - PDGF, chemotactic factors
- **Vasoactive mediators** - serotonin, tromboxans
- **Complement pathway activation**
- **Inflammatory leukocytes**
Inflammation

- **Infiltrating neutrophils** - bacteria phagocytosis, wound area cleaning

- **Macrophages** - phagocytosis of bacteria and tissue detritus, wound area cleaning, production of PDGF, Interleukins, CSGF-1, TGF-β, VEGF, FGF
Decrease in TNF-α and rise in TGF-β1 during wound healing

TNF-α
Inflammation

TGF-β1
Wound healing

Tkalcetic VI et al. 2007
Reepithelialization and Neovascularization (Day 5)

Tissue formation

Epidermis

Fibrin clot

Fibroblast

Granulation tissue

Blood vessel

Collagen

Dermis

Fat

Singer et al. NEJM 1999
Tissue formation

- **Formation of granulation tissue** - bacteria phagocytosis, wound area cleaning
- **Macrophages** - growth factors (PDGF, TGF-β, VEGF, IGF-1, FGF)
- **Extracellular matrix molecules** - GAG (hyaluronic acid)
- **Fibroblasts** - uPA (urokinase-type plasminogen activator), MMP 1, 2, 3, 13 (collagenase 1, gelatinase A, stromelysin 1, collagenase 3)
Epitelization

Vascularization of granular tissue

Clot

Granulation tissue

Singer et al NEJM 1999
Role of CCN proteins in wound healing

Leask A, Abraham DJ 2006
Role of CCN proteins in wound healing
Role of CCN proteins in wound healing

Leask A, Abraham DJ 2006
Local influences
Endothelial precursor cells (GATA pos.)

Keswani SG et al. 2004

- db/db
- STZ diabetes
- NOD diabetes

Control

+ PDGF-B

Keswani SG et al. 2004
Hyaluronan

✓ Hyaluronan is one of the most hygroscopic molecules in Nature.

✓ Hyaluronan concentration is elevated in foetal wounds.

✓ Hyaluronan leads to weakening of cell anchorage to extracellular matrix, allowing temporary detachment to facilitate cell division and migration.

✓ Hyaluronan controls ICAM mediated inflammatory activation

✓ Hyaluronan supports scarless healing
Pig model of granulation tissue formation

Infected complicated operation wound in pig
Granulation tissue formation effect of hyaluronan-iodine complex

Hyiodine®

Control
Deep wound in diabetic patient - hyaluronan iodine treatment

before

day 55

day 98

Wound contraction

Sobotka et al. 2007
Wound contraction - effect of hyaluronan iodine complex treatment
Wound contraction - effect of hyaluronan iodine complex treatment

Wound measured 9.3cm x 4.0 cm x 2.1 cm

Wound measured 3.0cm x 2.0 cm x 0.5 cm

After 12 weeks of Hyiodine treatment

Ajemian M. et al. 2007
Wound healing - effect of hyaluronan iodine complex treatment

Acute wound

Chronic wound

Ajemian M. et al. 2007
Systemic inflammation
Systemic inflammation

Inflammatory response

Stimulation of gluconeogenesis

Complex catabolic reaction with stimulated gluconeogenesis and insulin resistance: protein catabolism impaired operation wound healing
Systemic inflammation reduces nitrogen balance and wound healing

Nitrogen balance vs CRP

Cumulative nitrogen balance (g / 7d)

CRP (mg / l)
Psychological stress reduces wound healing


Fig. 1. Effect of restraint (RST) on wound healing: RST slowed wound healing. Beginning the day of wounding and continuing for 10 days, digital images of the wounds and a standard-sized dot on each mouse were collected. Wound size is expressed as the ratio of the wound area to the standard-sized dot for the home cage control (□) and the RST mice (●). Data represent the mean ± SE (n = five mice/group).
Psychological stress reduces wound healing

13 women taking care for dementia relatives
13 controls
3.5 mm experimental wound

Wound healing
Caregivers: 48.7 ± 2.9 days
Controls: 39.3 ± 2.9 days

Malignancy negatively influences wound healing

Inhibitors of wound healing were not tumor derived products.

Gatenby RA and Taylor DD 1990
Role of nutrition
Surgical wound healing is dependent of endogenous substrates

Undernutrition

Loss body cell mass

Deficit endogenous substrates for wound healing.

Complications (wound dehiscence, infections)
Undernutrition reduces wound healing

Baseline BMI versus length of stay for wound care provided by community nursing service. For each unit decrease in BMI, length of stay increased by a factor of 2.37 (adjusted $R^2 = 8.6\%$, $P = 0.046$).

Collins CE Nutrition 2005;21:147-155
Pressure ulcers

Systematic review 15 studies (1325 patients)

Enteral nutritional support, particularly high protein oral nutritional supplements significantly reduced the risk of developing pressure ulcers (to 25%).

Special substrates
Arginine

Arginine is suggested that supplements with arginine would improve wound healing.

Satriano J. 2003
Arginine

Arginine is suggestion that supplements with arginine would improve wound healing.

No effect in head and neck cancer wounds

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 21)</th>
<th>Arginine supplemented (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flap necrosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fistula</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Purulent drainage</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>28 ± 12</td>
<td>25 ± 12</td>
</tr>
</tbody>
</table>

Riso S et al. 2000
The possible role of arginine

A. Homeostasis

B. Early Phase

C. Transition Phase

D. Repair Phase

Satriano J. 2003
The possible role of arginine

Arginine is present in many nutrition supplements which would improve wound healing.

However affect of arginine on wound healing is complex - it can intensify or suppress wound healing.

At present time we have no one magic substrate which improves wound healing.
Thank you,
References


5. Leask A, Abraham DJ. All in the CCN family: essential matricellular signaling modulators emerge from the bunker J of Cell Sci 2006;119: 4803-4810


Key words

Wound healing, scar, inflammation, arginine, regeneration, hyaluronic acid