Understanding and Managing MMP’s in Wound Bed

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Learning Objectives

• Review the four sequential phases of normal wound healing and recognize the **BENEFICIAL** effects of **CONTROLLED INFLAMMATION** and **PROTEASE ACTIVITIES**

• Understand the link between **CHRONIC INFLAMMATION** caused by **PLANKTONIC** and **BIOFILM BACTERIA** and **ELEVATED PROTEASE ACTIVITIES** that **DESTROY** proteins that are essential to healing (extracellular matrix, growth factors, receptors)

• Understand the **VARIATION** of proteases and their **IMPACT** on wound healing

• Discuss current approaches to **MANAGEMENT AND REMOVAL** of proteases from the wound bed
Four Phases of Wound Healing

Four Phases of Wound Healing

<table>
<thead>
<tr>
<th>Injury</th>
<th>Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>3- 20 days</td>
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<tr>
<td></td>
<td>1 – 6 weeks</td>
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<tr>
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<td>6 weeks to 2 yrs</td>
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**Inflammation**
- Leukocyte migration
- Neutrophils
- Macrophages
- Release of growth factors

Controlled inflammation is beneficial

Matrix Metalloproteinases - MMPs
Necessary for Wound Healing

Debridement

Angiogenesis

Contraction

Epithelial Migration

Remodeling

MMPs in Normal Wound Healing

MMPs are essential for normal wound healing, **BUT** must be:

- At the right places
- At the right times
- At the right amounts
Venous Leg Ulcers are Inflammatory

Relative MMP Levels in Healthy Tissue and Leg Ulcer Tissue before and after Compression Therapy

![Graph showing relative MMP levels in healthy and ulcer tissue before and after compression therapy.](image)


Repeated Tissue Injury
Ischemia and Bioburden-Biofilm

Prolonged Elevated Inflammation
↑Neutrophils
↑Macrophages
↑Mast cells

Destruction of Essential Proteins
↑ECM degradation
↓Growth factors/receptors
↓Cell migration
↓Cell proliferation

Imbalanced Proteases and Inhibitors
↑Proteases
↓Inhibitors

Elevated MMP-1 in Venous Ulcers

Healing of Pressure Ulcers is Predicted by Protease Activity in Wound Fluids

**Graph:**
- **Good Healing:** >95% area healed; n=12
- **Intermediate Healing:** <95% but >65% area healed; n=36
- **Poor Healing:** <65% area healed; n=8

MMPs in Diabetic Foot Wounds

Expression of MMP-1, MMP-9 and TIMP-2

Sequential Degradation of the ECM

Chronic wounds typically show high levels of certain MMPs. These proteases sequentially degrade the native ECM, delaying healing.

First, collagenases (MMP1 and MMP8) cause the initial breakdown of the vital ECM structure.

Next, gelatinases (MMP2 and MMP9) further degrade the already-damaged ECM fragments into even smaller components.

MMP Wound Area Ratio

Patient A03 - MMP > 1.0 μg/ml and Slowly Healing

- MMP Time Line
- Wound Area Time Line

D. Gibson, Q. Yang, and G. Schultz. Description of MMP Activity Levels and Wound Surface Area Changes in Venous Leg Ulcers, SAWC Spring, May 2-4, 2013 Denver, CO.
MMP-9 Activity Correlates With Wound Healing Time Course

Biofilms Identified in $>80\%$ of Biopsies of Chronic Wounds but in Only $6\%$ of Acute Wounds


Question: How do biofilms impair healing of skin wounds?

Answer: Biofilms stimulate chronic inflammation by increasing release of proinflammatory cytokines which leads to highly increased levels of proteases and reactive oxygen species that degrade proteins which are essential for healing.
Effects of Antimicrobial Agents on Mature Biofilms on Pig Skin Explants

Conclusion: Inflammation in chronic wounds must be reduced to levels that lead to low protease activities which will allow wounds to heal.

Action: Bacterial levels (both planktonic and biofilm) must be reduced for healing.
Addressing MMP’s in the Wound Bed

- Debridement
- Sacrificial substrate
- Negative pressure
- Sponge effect
- Drugs
- Compression
- TIMP’s
- Themselves
Step-Down-Step-Up Treatment for Chronic Wounds

Initiate multiple therapies in combination

Aggressive debridement
Empirical topics: antiseptics and systemic antibiotics
Manage host factors (off-loading, compression, diabetes, nutrition)
DNA identification of microorganisms and point-of-care diagnostics

~days 1-4

Optimize personalized therapy according to healing status
Assess inflammation and healing status
Appropriate debridement
Optimize /personalize topical antiseptics and Continue management of host factors

~days 5-7

De-escalate treatment as wound improves
Assess inflammation and healing status
Maintenance debridement
Re-evaluate need for topical antiseptics and systemic antibiotics
Continue management of host factors

~1-4 weeks

Evaluate wound healing and decide

Step up to advanced therapies
Advanced therapies:
• Growth factors
• Skin grafts
• Combination products

Standard care

Continue until healed

Standard care
New Research
Confusing / Complicated

• A trial showed **COLLAGEN** may not reduce MMP activity

• In vitro proteinases rapidly lose activity, likely due **AUTOLYSIS**
  • Introduction of protein **PROTECTS** the proteinases and increase half-life

• Competitive inhibition via protein **IS NOT** supported by this study

• MMP activity **CAN PREDICT FAILURE** of progression week to week

• Proteinases are **NOT THE ONLY** source of failure
Conclusion

- Must address **PLANKTONIC BACTERIA AND BIOFILM**
  - Planktonic
  - BIOFILM
- A severe impact of **BIOFILM IS TO DRIVE PROTEASE ELEVATION**
  - INFLAMATION
- **UTILIZATION OF MULTIPLE** modalities to lower MMP
  - COMBINATION THERAPIES
- Utilization of the **STEP UP → STEP DOWN** treatment protocol
Thank You