Antibiotics as Immunomodulators

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Baylor College of Medicine
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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Ted Rosen, MD
F120 Treating Tumors and Inflammatory Skin Diseases with Immunomodulators and Biologics

DISCLOSURES
I do not have any relevant relationships with industry.
Janus: The God of Two Faces
Antibiotics = Immunosomodulators?

- Major property of molecule: Kill susceptible microbes
- Ancillary property of molecule: Immunomodulation (example)
- Drug administered to take advantage of ancillary property
- Also...some conditions are suspected of being infectious in nature, although not proven. Therefore, hedging bets!
  - Rosacea
  - Sarcoidosis
Antibiotics = Immunomodulators?

- Major property of molecule
- Ancillary property of molecule
- *Drug administered to take advantage of ancillary property*
- Also….some conditions are suspected of being infectious in nature, although not proven. Therefore, hedging bets!
  - Rosacea: Demodex or bacteria living within Demodex
  - Sarcoidosis: Atypical (Environmental) mycobacteria
Rosacea Pathogenesis

Pathogenesis of Rosacea

**Immune Detection Dysfunction Underscores Rosacea-affected and Rosacea-prone Facial Skin**

**TRIGGERS**
- Heat
- Wind
- Trauma
- UV exposure
- Steroids
- Demodex?
- Microbes?
- Other?

**Increase in TLR2 on Keratinocytes**
(Augmented “Danger” Recognition)

**Elevated Cathelicidin Precursor**
(hCAP18)

**Serine Protease**
(Kallikrein-5 [KLK-5])

**Pro-Serine Protease**
(Pro-KLK-5)

**Increased LL-37 + Variant Peptides**

**ROSACEA**
Inflammation / Neurovascular Effects / Vascular Changes / Fixed Physical Changes in Cutaneous Vasculature

**MMP**

*TLR2
Toll-like receptor-2*

References:
- Int J Mol Sci. 2016 Sep 15;17(9).E1562
TETRACYCLINE DERIVATIVES HAVE MULTIPLE ANTI-INFLAMMATORY PROPERTIES

Pharmacol Res 2011;63:130-45

↓ NO Production and Activity
↓ ROS
↓ MMPs
↓ Phospholipase A2
↓ Angiogenesis
↓ Granulomatous Inflammation
↓ Proinflammatory Cytokine release
↓ Cellular Migration, Proliferation
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Pro-Serine Protease

Tetracycline Drugs

Percent In-vitro inhibition of cutaneous collagenase (MMP-8) by Tetracycline Family

![Graph showing the inhibition of collagenase by different drugs at various concentrations.](image-url)
Percent In-vitro inhibition of cutaneous collagenase (MMP-8) by Tetracycline Family

Strongest inhibition of MMPs by Doxycycline
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**ROS**

**MMP**

**ROSACEA**
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*TLR2 Toll-like receptor-2

**References**

*Br J Dermatol 2007;157:1124-31*
How are ROS tied to Antibiotics?

• ROS are elevated in rosacea skin compared to normal

• Tetracycline family significantly reduces ROS

• There is a hierarchy to this property. Minocycline > Doxy > TCN
  - J Neurochem 2005;94:819-27

• Tetracyclines reduce ROS by....
  • Neutrophil inhibition
  • Direct scavaging of free radicals
  • Chemical reactions generating ROS specifically blocked (eg iNOS)
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- Doxy, Mino

ROSACEA

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Azithromycin and Rosacea?

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- Arch Dermatol 2004;140:489-90
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Azithromycin as an immunomodulator

Int J Antimicrob Agents 2008;31:12-20

- Semi-synthetic analogue of erythromycin; Targets 23S ribosomal RNA
- Excellent tissue penetration, low toxicity, long half-life
- Rapid selective uptake in neutrophils, macrophages, fibroblasts
- Degranulation of neutrophils; Inhibits neutrophil chemotaxis
- Decreases expression of pro-inflammatory cytokines (IL-6, IL-8, TNF-alfa)
- Decreases expression of pro-inflammatory transcription (NF-κβ)
- Decreases, selectively, matrix metalloproteinases (MMP-2,9)

J Pharmacol Exp Ther 2000;292:156-63
Eur J Pharmacol 2002;450:277-89
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**Chemotaxis**

**Vasodilation**

**Neoangiogenesis**

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Topical Ivermectin 1% Cream
• Approved 12-23-2014
• QD treatment for rosacea
• Better than metronidazole 0.75%
• Compares favorably to azelaic acid 15%
• Killing Demodex? Bacteria in Demodex?
• OR…..is it anti-inflammatory?????
Ivermectin is Anti-inflammatory!

- Decreases expression of pro-inflammatory transcription (NF-κβ) in vitro
- Inhibits LPS-induced TNF-α, IL-1b and IL-6 in vitro and in vivo
- Reduces chemotaxis of neutrophils and lymphocytes in vivo
- Inhibits LPS-induced Nitric oxide and iNOS mRNA in vitro and in vivo
- Upregulates IL-10 (anti-inflammatory activity) in vitro
- Inhibits COX-2 activity and PGE2 production in vitro

Inflamm Res 2011;60:589-96
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Vasodilation
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[References]
Sarcoid: Novel Rx (“CLEAR”)

Eight weeks, Active (n=11) versus Placebo (n=11)

Concomitant:

- Levofloxacin 750mg Day 1, then 500mg/d
- Ethambutol 25mg/kg/d (maximum 1200mg/d)
- Azithromycin 500mg Day 1, then 250mg/d
- Rifampin 10mg/kg/d (maximum 300mg/d)

Active had > decrease (vrs increase) in target lesion size and severity
Sarcoid and the “CLEAR” Therapy

- **Levofloxacin**
  - Inhibits cellular phosphodiesterase, elevates cAMP
  - Reduces synthesis of IL-1β, IL-8, TNF-alfa by inhibiting NF-κβ
    - Lancet Infect Dis 2003;3:359-71

- **Ethambutol**
  - Apoptosis of activated lymphocytes
    - Antibiot Khimioter 2010;55:25-29

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- **Rifampin**
  - Inhibits TNF-alfa secretion
  - Enhances IL-10 secretion
    - J Chemother 2004;16:357-61

References:

- JAMA Dermatol 2013;149:1040-49
- Sarcoidosis Vasc Diffuse Lung Dis 2013;30:201-11
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    • J Chemother 2009;21:396-402

• **Rifampin**
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Sarcoidosis and Minocycline

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<th>Reference</th>
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<tr>
<td>JAMA Dermatol 2013;149:758-60</td>
<td>20 of 27</td>
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<td>J Drugs Dermatol 2012;11:385-89</td>
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<td>Clin Rheumatol 2008;27:1195-97</td>
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<td>Arch Dermatol 2001;137:69-73</td>
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<td>Skin only</td>
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</table>

Multiple mechanisms whereby minocycline might be anti-inflammatory in sarcoid (such as ↓TNF-alfa and others, it also directly inhibits granuloma formation). Arch Derm 1994;130:748-52
Sarcoidosis and Minocycline Monotherapy
Orofacial Granulomatosis

• Primary
  • Melkersson-Rosenthal Syndrome
  • Granulomatous cheilitis

• Secondary
  • Tuberculosis
  • Sarcoid
  • Crohn’s Disease
  • Solid Facial Edema
Orofacial Granulomatosis: Inflammatory Dis

- CD4+ Cellular infiltrate
- Increased Th1 cells
- Increased INF-γ, IL-12, TNF-α
Orofacial Granulomatosis: Antibiotic Rx
Is success due to anti-inflammatory activity?

- Minocycline
  - Dermatology. 1992;185:220

- Azithromycin and Roxithromycin
  - JAMA Dermatol. 2015;151: 219–220
Orofacial Granulomatosis: Antibiotic Rx
Is success due to anti-inflammatory activity?

Azithromycin 500mg QD x 3 days each week (3 rounds)
Orofacial Granulomatosis: Antibiotic Rx
Is success due to anti-inflammatory activity?

Azithromycin 500mg QD x 3 days each week (6 rounds)
I hope I have “unmasked” some antibiotic properties with which you might NOT have been so familiar!
Thanks for your attention!

- Ted Rosen, MD
- Professor of Dermatology
- Baylor College of Medicine
- Houston, Texas