PROPOLIS ANTIBACTERIAL MECHANISMS: NEW INSIGHTS

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BACKGROUND

OVERALL, IN VITRO ANTIBACTERIAL ACTIVITY DATA SUPPORT THE THEORY THAT PROPOLIS IS LESS ACTIVE THAN TOPICAL ANTIBIOTICS AGAINST THE MOST FREQUENT PATHOGENS ISOLATED FROM CHRONIC SKIN WOUNDS AND FROM BURNS

best MICs in mcg/mL	
propolis 84	antibiotics 0.5

NEVERTHELESS, SINCE ANCIENT TIMES, IN VIVO TOPICAL PROPOLIS HAS SHOWN VERY GOOD ANTIINFECTIOUS EFFICACY IN THE TREATMENT OF THE ABOVE CONDITIONS

BACKGROUND

IN VITRO DATA WERE OBTAINED FROM:

- **STUDIES WITH 63 EEP SAMPLES COLLECTED IN THE 5 CONTINENTS AND TESTED AGAINST**
  - **237 Staphylococcus spp**
  - **175 Streptococcus spp**
  - **19 Ps. aeruginosa**
- **8 PUBLISHED PAPERS**

1) SEIDEL,V Phytoter Res (2008); 2) DRAGO, L J Appl Microbiol (2007); 3)SCAZZOCCHIO, F Microbiol Res (2006); 4) FERNANDES JUNIOR, A Mem Inst Oswaldo Cruz (2005); 5) PEPELJNJAK, S Fems Microbiol Lett (2004); 6) SERRA, J Z Naturforsch (2000); 7) BOSSIO, K Lett Appl Microbiol (2000); 8) GRANGE, JM J R Soc Med (1990)

RATIONALE

OUR AIM WAS TO ANSWER ONE QUESTION

WHY IS PROPOLIS AN EFFECTIVE TOPICAL ANTIINFECTIOUS AGENT IN VIVO IN SPITE OF ITS LOW ANTIBACTERIAL ACTIVITY IN VITRO ?

METHODS

LOOKING FOR PROBABLE FUNCTIONAL RELATIOSHIPS BETWEEN PROPOLIS AND INNATE IMMUNE SYSTEM MECHANISMS, WE PERFORMED A MEDLINE-BASED BIBLIOGRAPHIC SEARCH USING THE KEY TERMS

PROPOLIS AND FLAVONOIDS LINKED WITH

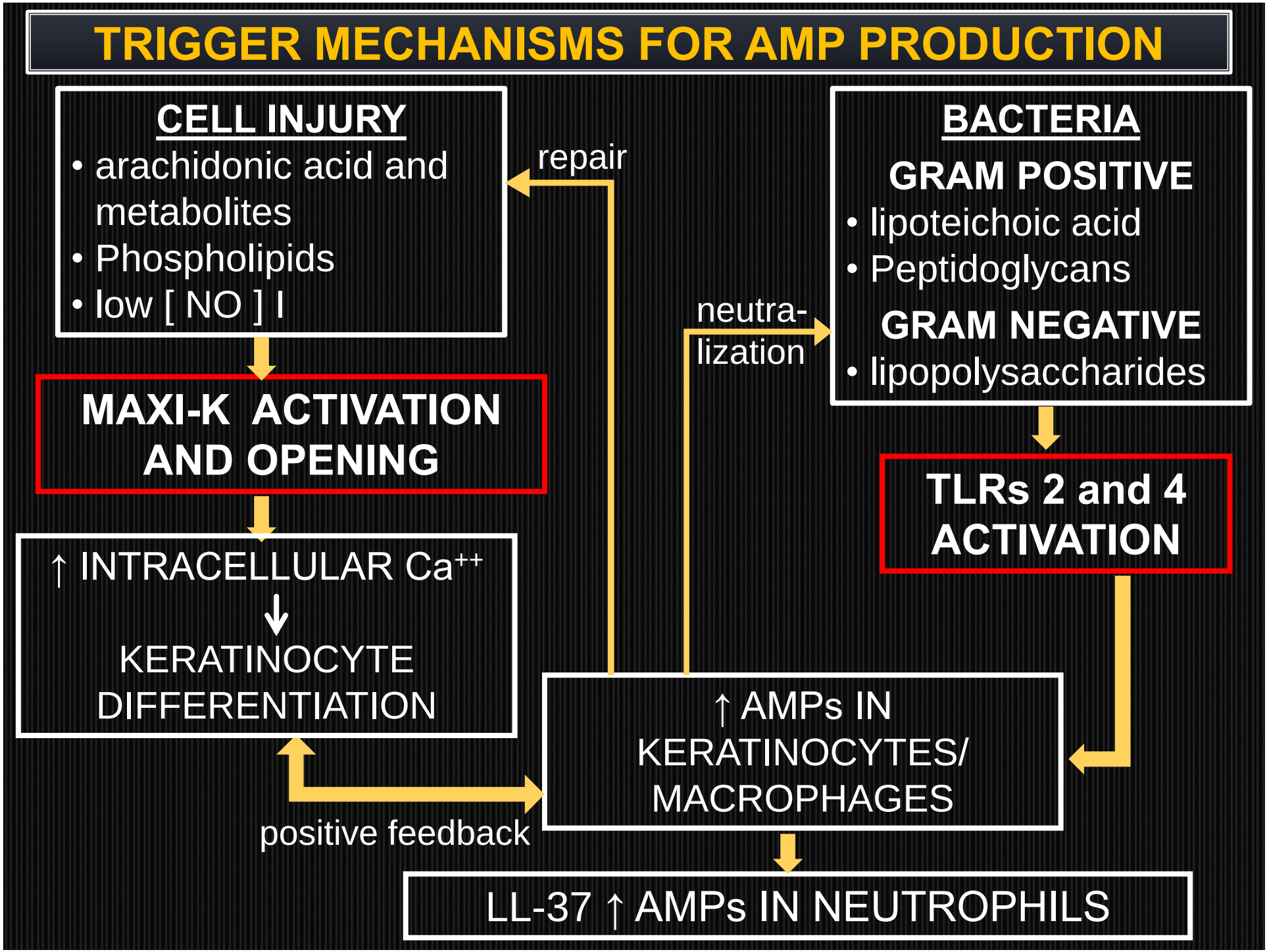
- antibacterial – anti-inflammatory – antioxidant
- host antimicrobial skin peptides - AMPs
- large conductance calcium-activated potassium channels – Maxi-K or BK_{Ca} channels
- Toll-like receptors (recognize pathogen-associated molecules)– TLRs

ANTIMICROBIAL PEPTIDES

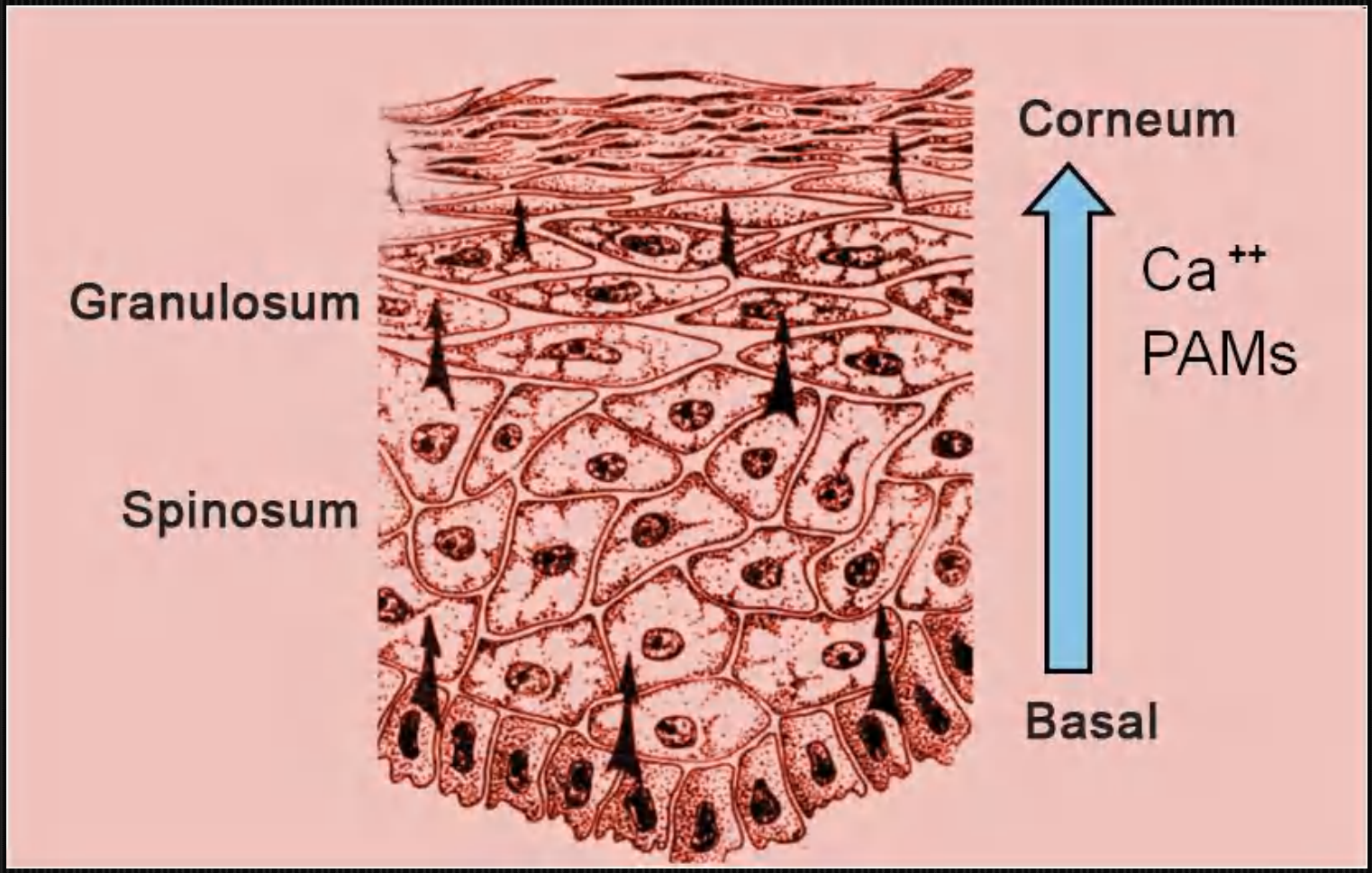
HIGHLY-CONSERVED ANCESTRAL MOLECULES OF THE INNATE IMMUNE SYSTEM WHICH FORM A CHEMICAL PROTECTIVE BARRIER IN SKIN

- Cathelicidin LL-37 and human Beta Defensins (4) produced by keratinocytes, neutrophils and macrophages.
- Human Neutrophil Peptides (4) produced by neutrophils.
- Collectively display broad antimicrobial spectrum activity and high endotoxin neutralization capacity.
- Expression is readily induced after acute skin injury, infection or inflammation.
- Expression is strongly reduced in the bed of chronic skin wounds and in burns but preserved at its borders.

BERNARD and GALLO, Cell Mol Life Sci (2011), SCHRÖDER and HARDER, Cell Mol Life Sci (2006)


TRIGGER MECHANISMS FOR AMP PRODUCTION
CELL INJURY
• arachidonic acid and metabolites
• Phospholipids
• low [NO] I
repair
BACTERIA
GRAM POSITIVE
• lipoteichoic acid
• Peptidoglycans
GRAM NEGATIVE
• lipopolysaccharides
neutra-lization
MAXI-K ACTIVATION AND OPENING
TLRs 2 and 4 ACTIVATION
↑ INTRACELLULAR Ca++
KERATINOCYTE DIFFERENTIATION
↑ AMPs IN KERATINOCYTES/ MACROPHAGES
positive feedback
LL-37 ↑ AMPs IN NEUTROPHILS

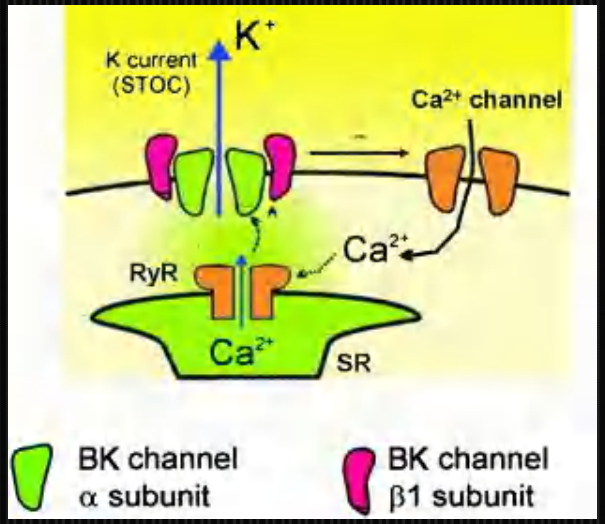
EPIDERMAL DIFFERENTIATION



strong increase of AMPs as Ca^{++} driven differentiation progresses

MAURO, T et al J Invest Dermatol (1997)

PROPOLIS, MAXI- K CHANNELS AND AMP PRODUCTION



DIRECT EFFECT : propolis flavonoids – apigenine, kaempferol, quercetin, hesperitin, naringenin – and CAPE are pharmacological Maxi –K activators (openers) and could increase AMP production.

INDIRECT EFFECT: in chronic skin wounds and in burns the strong antioxidant activity of propolis can protect the Maxi-K channels structural proteins from the documented damage caused by high levels of ROS and RNS, thus preserving AMP production.

TANG,XD (2004), LIU, Y (2002); XU, YC (2008); KUHLMANN, CR (2005); ERDOGAN, A (2007); NARDI, A (2008); SHIEH, DB (2005)

PROPOLIS AND TOLL-LIKE RECEPTORS

IT IS DOCUMENTED THAT PROPOLIS CAN ACTIVATE THE INITIAL STEPS OF THE IMMUNE RESPONSE AGAINST INFECTION BY INCREASING THE EXPRESSION OF TLR-2 AND -4 IN PERITONEAL MACROPHAGES AND IN SPLEEN CELLS AFTER STRESS-INDUCED IMMUNOSUPPRESSION

DUE TO ITS ANTIOXIDANT ACTIVITY, TOPICAL PROPOLIS CAN PROTECT THE TLR STRUCTURAL PROTEINS FROM THE DAMAGE CAUSED BY THE HIGH LEVELS OF ROS, RNS AND PROTEOLYTIC ENZYMES IN CHRONIC SKIN ULCERS AND IN BURNS, THUS PRESERVING TLR FUNCTIONAL CAPACITY

HARDER, J J Invest Dermatol (2004); ORSATTI, CL Phytother Res (2010) and Nat Prod Res (2011); PAGLIARONE , AC Int Immunopharmacol (2009)

PROPOLIS AND BACTERIAL VIRULENCE FACTORS

- FLAVONOIDS, AS EFFICIENT CHELATING AGENTS, DECREASE IRON BIOAVAILABILITY, AN ESSENTIAL NUTRIENT FOR P.AERUGINOSA SURVIVAL AND VIRULENCE
- PROPOLIS ABROGATED S.AUREUS COAGULASE ACTIVITY AND DECREASED BY 17 - 50% STAPH.SPP LIPASE ACTIVITY, ENZYMES RELATED WITH HOST TISSUE DAMAGE
- BIOFILMS, HIGHLY RESISTANTANT TO ANTIBIOTICS AND PHAGOCYTOSIS POLYMICROBIAL AGGREGATES IN CHRONIC SKIN ULCERS AND IN BURNS, WERE SIGNIFICANTLY REDUCED BY PROPOLIS (S.AUREUS) AND BY LL – 37 (S.EPIDERMIDIS AND P.AERUGINOSA)

HAVSTEEN, BH (2002); SCAZZOCCHIO, F (2006); OVERHAGE, J (2008); HELL, E (2010)

CONCLUSIONS

PROPOLIS TOPICAL ANTIINFECTIOUS EFFICACY COULD BE THE CONSEQUENCE OF:

- **ITS ANTIBACTERIAL ACTIVITY AND**
- **ITS FUNCTIONAL RELATIONSHIPS WITH THE INNATE IMMUNE SYSTEM**
  1. **INCREASED PRODUCTION OF SKIN AMPs THROUGH THE ACTIVATION OF MAXI – K CHANNELS**
  2. **INCREASED TLR EXPRESSION**