Bacteria and pain

--- The Direct Regulatory Effect of Bacteria on Nociception

Student: Wang Daijuanru Wanda
(1st year Mphil student)
Supervisor: Prof. Zigui Chen
Date: 16/12/2021
Department of Microbiology

Core Paper

- Chiu IM, Heesters BA, Gh

ARTICLE

doi:10.1038/nature12479

Bacteria activate sensory neurons that modulate pain and inflammation

Isaac M. Chiu[1], Balthasar A. Heesters[2,3], Nader Ghasemlou[1], Christian A. Von Hehn[1], Fan Zhao[4], Johnathan Tran[1], Brian Wainger[1], Amanda Strominger[1], Srirat Muralidharan[1], Alexander R. Horswill[5], Juliane Bubeck Wardenburg[6], Sun Wook Hwang[1,7],

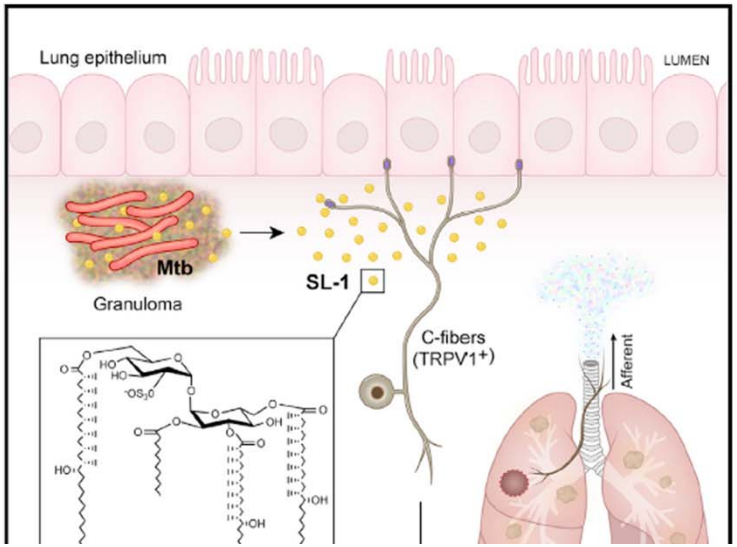
Article

zed to detect potentially damaging stimuli, protecting the organism by initiating fensive behaviours. Bacterial infections produce pain by unknown molecular ned to be secondary to immune activation. Here we demonstrate that bacteria the immune response mediated through TLR2, MyD88, T cells, B cells, and sary for *Staphylococcus aureus*-induced pain in mice. Mechanical and thermal

Cell

Mycobacterium tuberculosis Sulfolipid-1 Activates Nociceptive Neurons and Induces Cough

Graphical Abstract



Autho
Cody F
Haaris
Theodo

Corre
michae

In Brie
Mycob
glycoli
trigger
neuron

Cell

Mycobacterial Toxin Induces Analgesia in Buruli Ulcer by Targeting the Angiotensin Pathways

Estelle Marion,[1,2,13] Ok-Ryul Song,[1,2,3,13] Thierry Christophe,[2,13] Jérémie Babonneau,[2] Denis Fenistein,[2] Joël Eyer,[4] Frank Letournel,[4] Daniel Henrion,[5] Nicolas Clere,[6] Vincent Paille,[5] Nathalie C. Guérineau,[5] Jean-Paul Saint André,[7] Philipp Gersbach,[8] Karl-Heinz Altmann,[8] Timothy Paul Stinear,[9] Yannick Comoglio,[10] Guillaume Sandoz,[10] Laurence Preisser,[11] Yves Delneste,[11] Edouard Yeramian,[12,14] Laurent Marsollier,[1,2,11,14,*] and Priscille Brodin[2,3,14,*]
[1]Inserm Avenir, 4 rue Larrey 49, 933 Angers, France
[2]Inserm Avenir, Institut Pasteur Korea, 16, Daewangpangyo-ro 712 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 463-400, Korea
[3]Inserm U1019, CNRS UMR8204, Université de Lille - Nord de France, Institut Pasteur de Lille, Center for Infection and Immunity, 1, rue du Professeur Calmette, 59000 Lille, France
[4]UPRES - EA 3143, Laboratoire de Neurobiologie et Transgénèse, 4 rue Larrey 49, 933 Angers, France

Presentation Outline

01 Pain in bacterial infection

02 Bacteria directly modulate pain

- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*
- *Mycobacterium ulcerans*

03 Clinical significance

04 Conclusion

Part 01

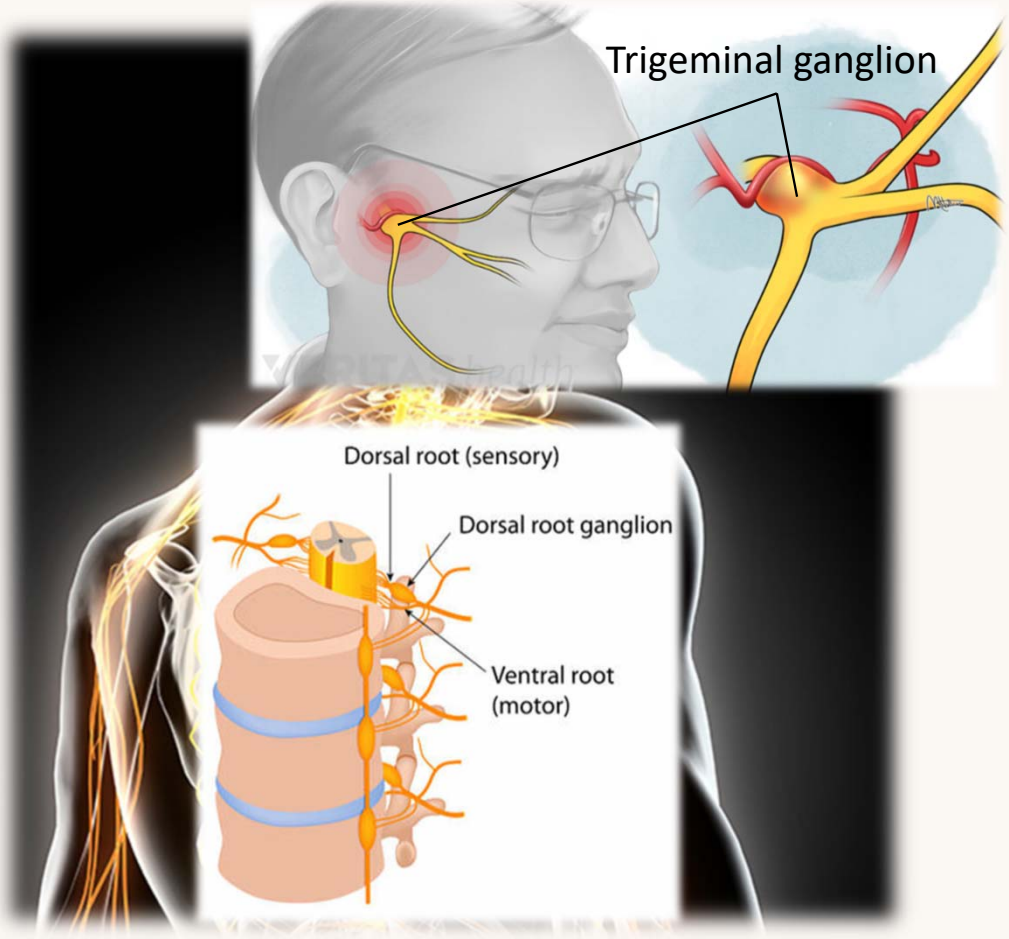
Pain in bacterial infection

Nociception: The occurrence of pain

- Bacterial infection is often painful.
- Pain is a defense mechanism against threats.
- Intense temperature, mechanical & chemical stimuli activate **nociceptor**

(Deng and Chiu. *PLoS Pathog*. 2021., Basbaum and Jessell. *Principles of Neural Science*. 2000)

Nociceptor



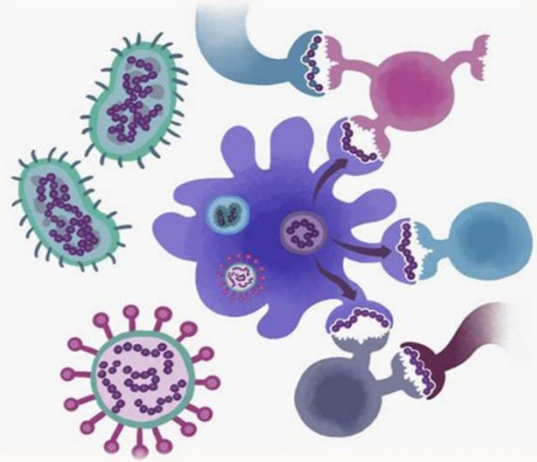
- Subpopulation of peripheral nerve fibers
- Location of the cell body:
  - Dorsal root ganglia for the body (DRG)
  - Trigeminal ganglion for the face
- Nociceptors are excited only when stimulus intensities reach the noxious range

(Basbaum and Jessell. *Principles of Neural Science.* 2000., Chiu et al. *Nature*. 2013)

Bacteria modulate pain

Bacterial infections produce pain secondary to immune activation

Bacteria modulate pain through directly activating nociceptors



Staphylococcus aureus

Mycobacterium tuberculosis

Mycobacterium ulcerans

(Deng and Chiu. *PLoS Pathog.* 2021., Chiu et al. *Nature*. 2013)

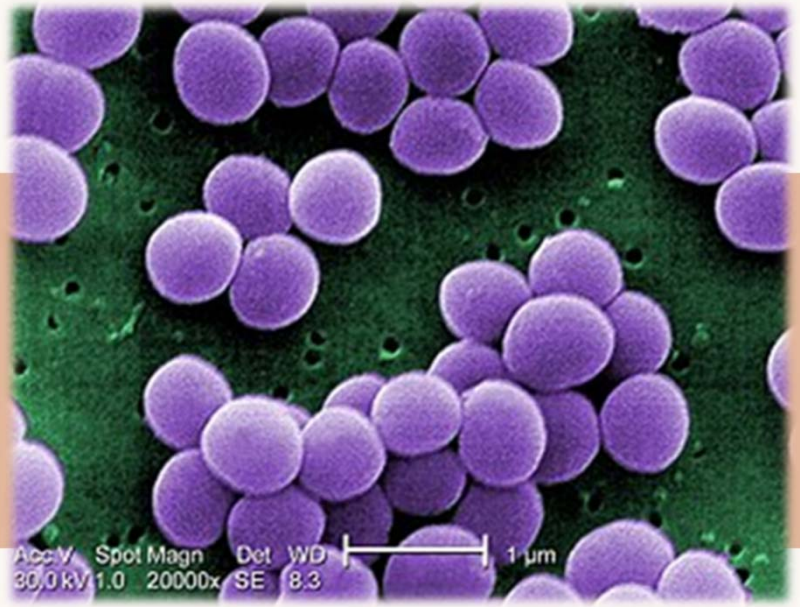
Part 02

Bacteria directly modulate pain

- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*
- *Mycobacterium ulcerans*

01

Staphylococcus aureus



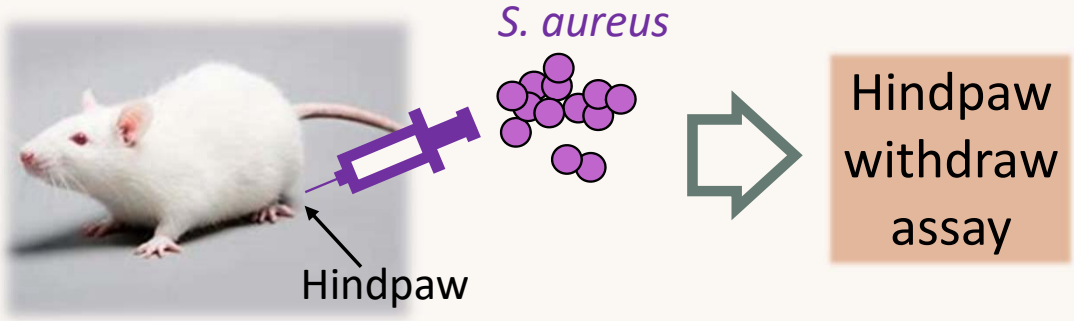
A major cause of wound and surgical infections

- Painful abscesses, cellulitis and necrotizing fascitis.
- Releases toxins to cause bacterial dissemination and tissue damage

(Chiu et al. *Nature*. 2013)

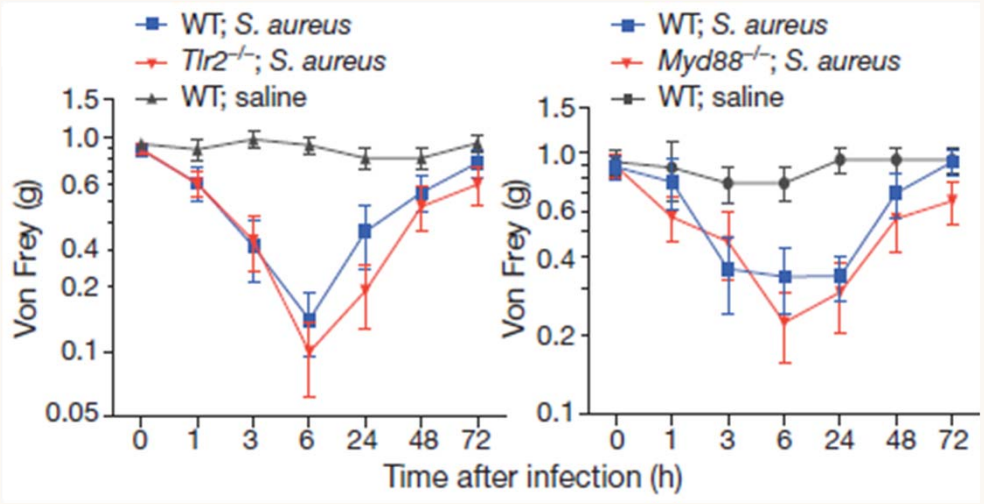
S. aureus produce pain independently from host defense

WT *or Tlr2*-/- or *Myd88*-/- mice



Hindpaw withdraw assay

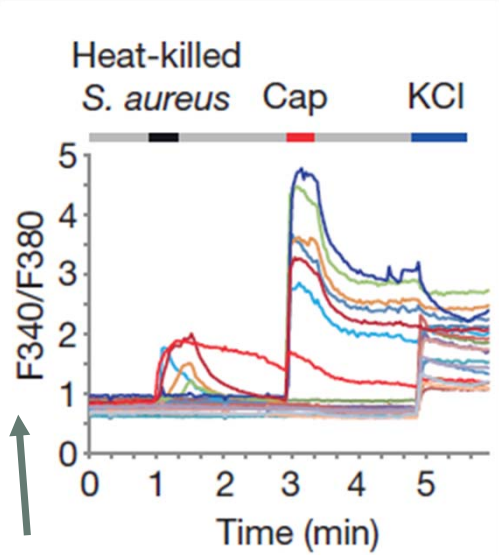
- Reduced mechanical stimuli threshold for both WT and immune deficiency mice

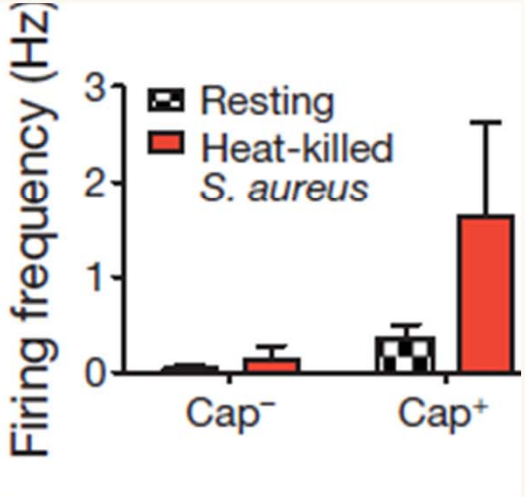


S. aureus produce pain directly through activating sensory neurons, distinct from immune response mechanisms

(Chiu et al. *Nature*. 2013)

S. aureus components activate nociceptors





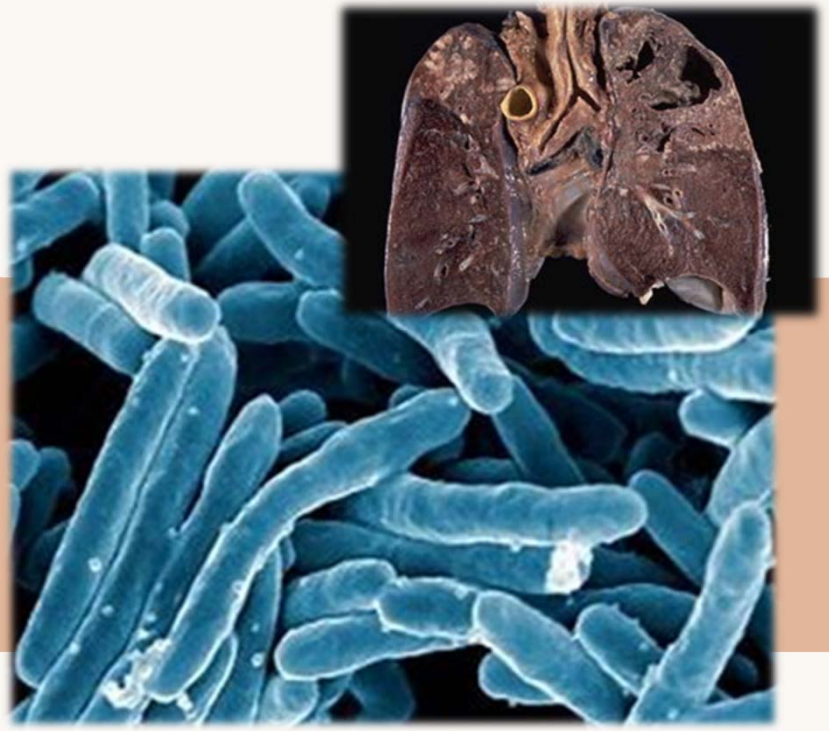
- Heat-killed S. aureus induced a calcium flux response and action potential firing in capsaicin-responsive DRG neurons

Heat-stable molecular elements from S. aureus activates nociceptors and leads to pain

(Chiu et al. *Nature*. 2013)

02

Mycobacterium. tuberculosis (Mtb)



Pulmonary tuberculosis

- Persistent cough and have high transmission ability
- The cough reflex can be triggered by nociceptive neurons innervating the lungs

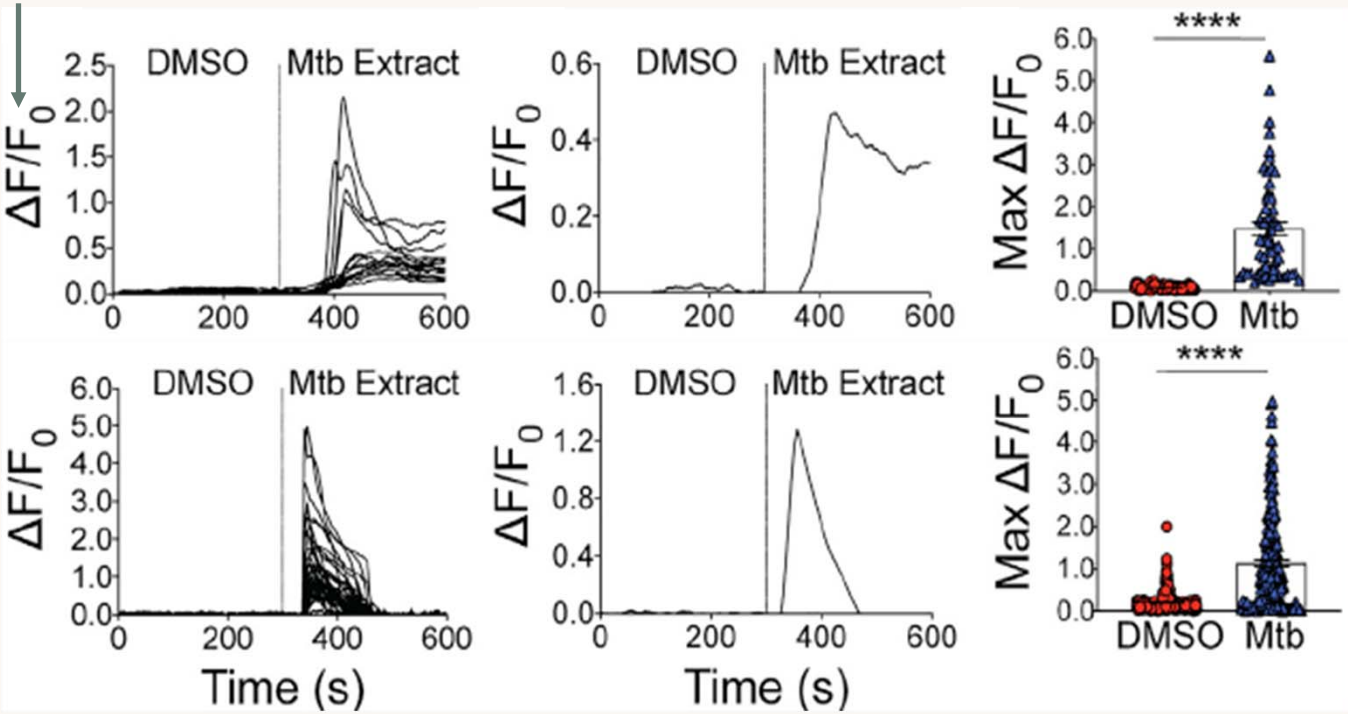
(Ruhl et al. *Cell*. 2020)

Mtb Extract activates Nociceptive Neurons

Intracellular
[Ca2+]

Primary mice
DRG neurons

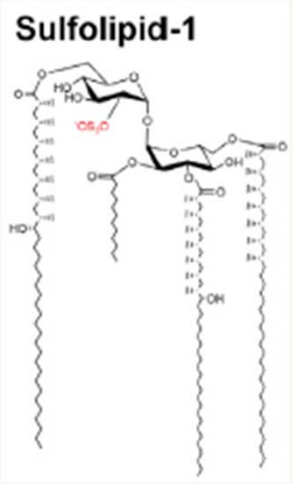
Primary human
DRG neurons



(Ruhl et al. *Cell*. 2020)

Virulent *Mtb* component activates nociceptive neurons

Compound	Triggers Increased $[Ca^{2+}]$
DMSO	–
Capsaicin	+
M. canettii total lipids	+
H37Rv total lipids (normoxic)	+
H37Rv total lipids (hypoxic)	+
CDC1551 cell membrane extract	–
HN878 cell membrane extract	–
H37Rv cell membrane extract	–
CDC1551 cytosol fraction	–
H37Rv cytosol fraction	–
H37Rv soluble cell wall proteins	–
H37Rv TX-114 soluble proteins	–
H37Rv purified lipoarabinomannan (LAM)	–
CDC1551 culture filtrate proteins	–
HN878 culture filtrate proteins	–
Sulfolipid-1	+
Trehalose monomycolate	–
Trehalose dimycolate	–
C24:1 mono-sulfo-galactosyl(β) ceramide (d18:1/24:1)	–
Galactocerebroside	–
H37Rv phosphatidylinositol mannosides 1 & 2 ($PIM_{1,2}$)	–
H37Rv phthiocerol dimycocerosate (PDIM)	–



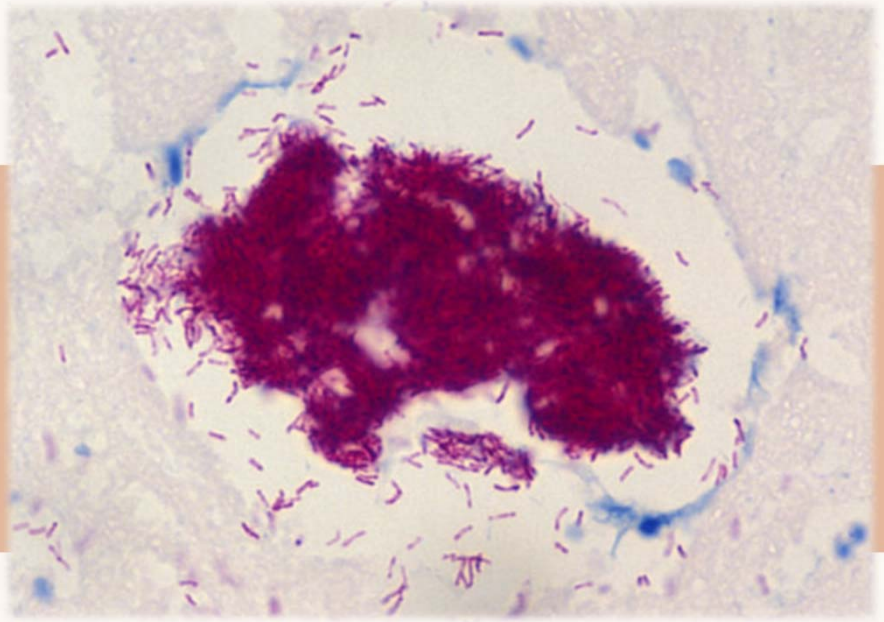
Molecular structure of SL-1

- SL-1 is the most abundant sulfated glycolipid located in the outer membrane and cell wall of mycobacteria
- Unique to pathogenic mycobacteria

Unique component in Mtb extraction directly leads to nociception

(Ruhl et al. *Cell*. 2020)

Mycobacterium ulcerans (M. ulcerans)

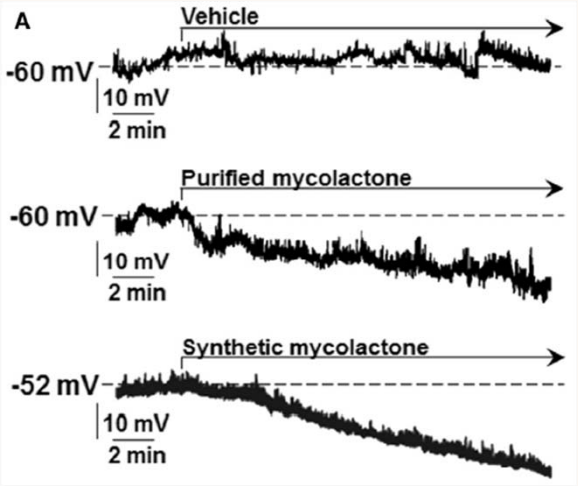


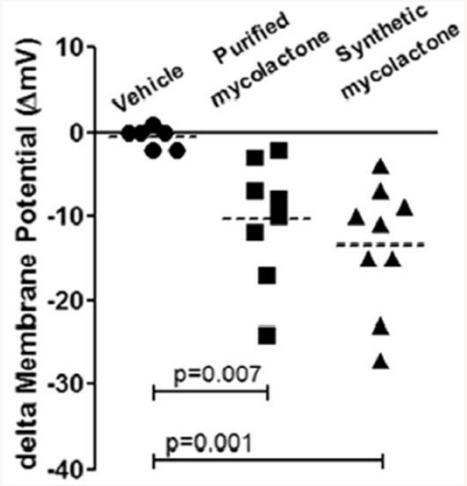
The pathogenic agent of Buruli ulcer

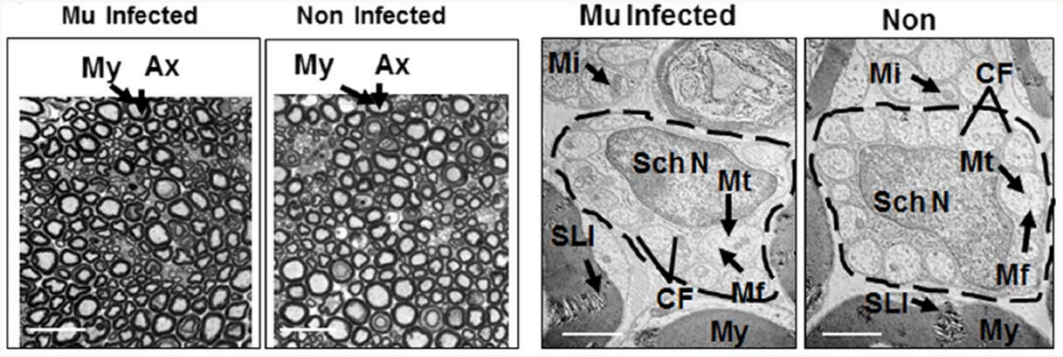
- Cause extensive skin lesions **NOT** accompanied by pain
- Previously thought:
  Direct nerve cell destruction

(Marion et al. *Cell*. 2014)

Mycobacterial toxin directly induces analgesia



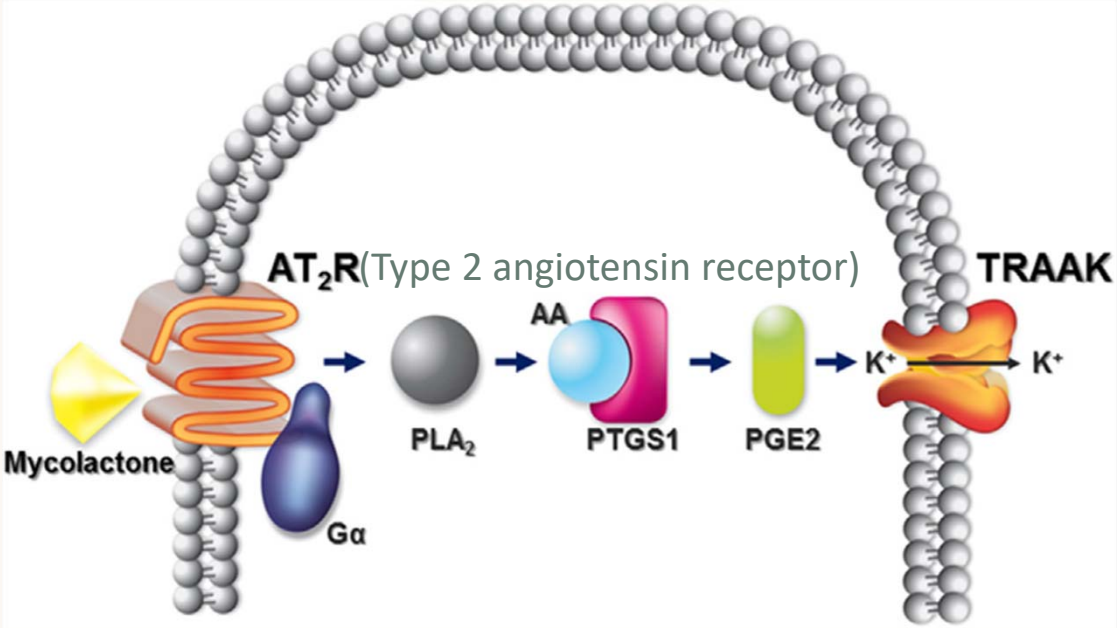




- Mycolactone induce hyperpolarization
- No signs of nerve degeneration after infection

(Marion et al. *Cell*. 2014)

Mycolactone elicits signaling through AT2Rs



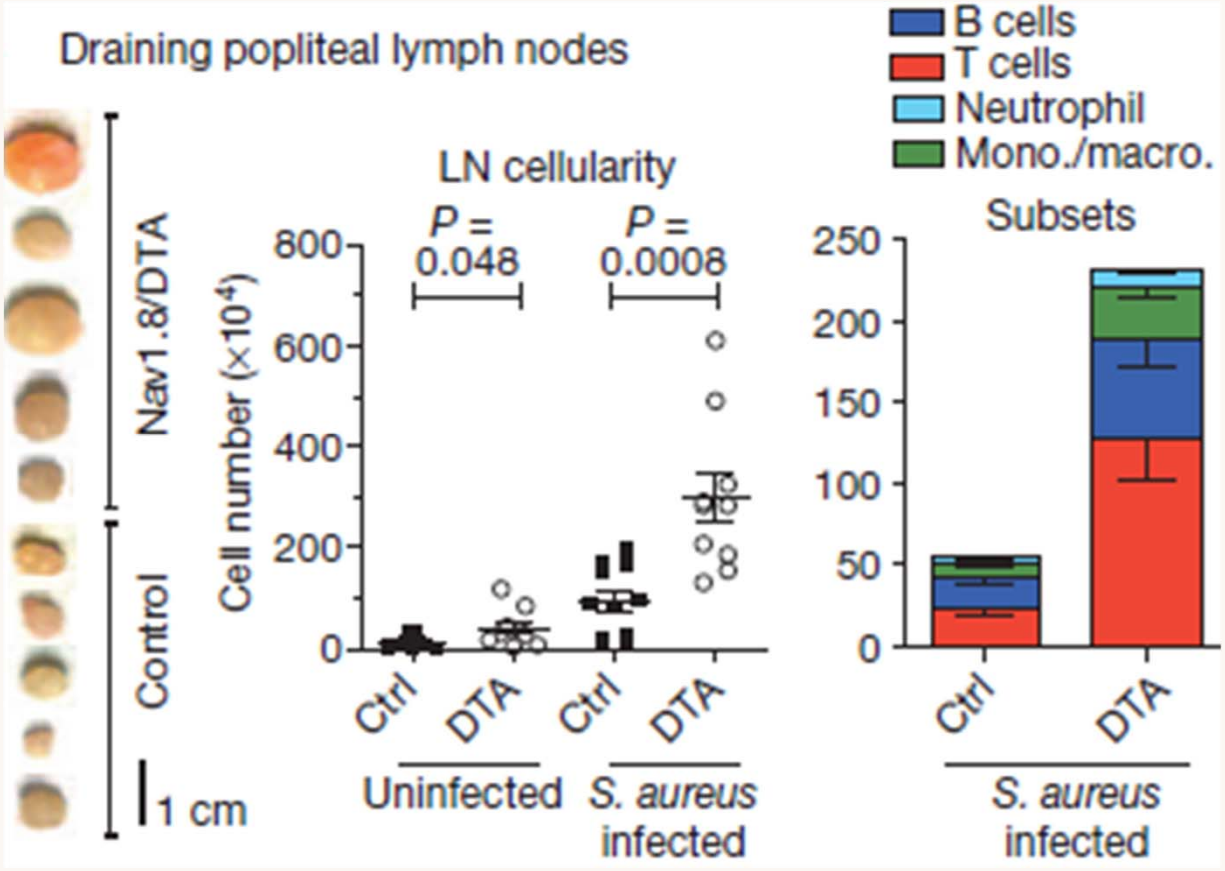
M.ulcerans secreted mycolactone induces pain loss directly by targeting the angiotensin pathways

(Marion et al. *Cell*. 2014)

Part 03

Clinical significance

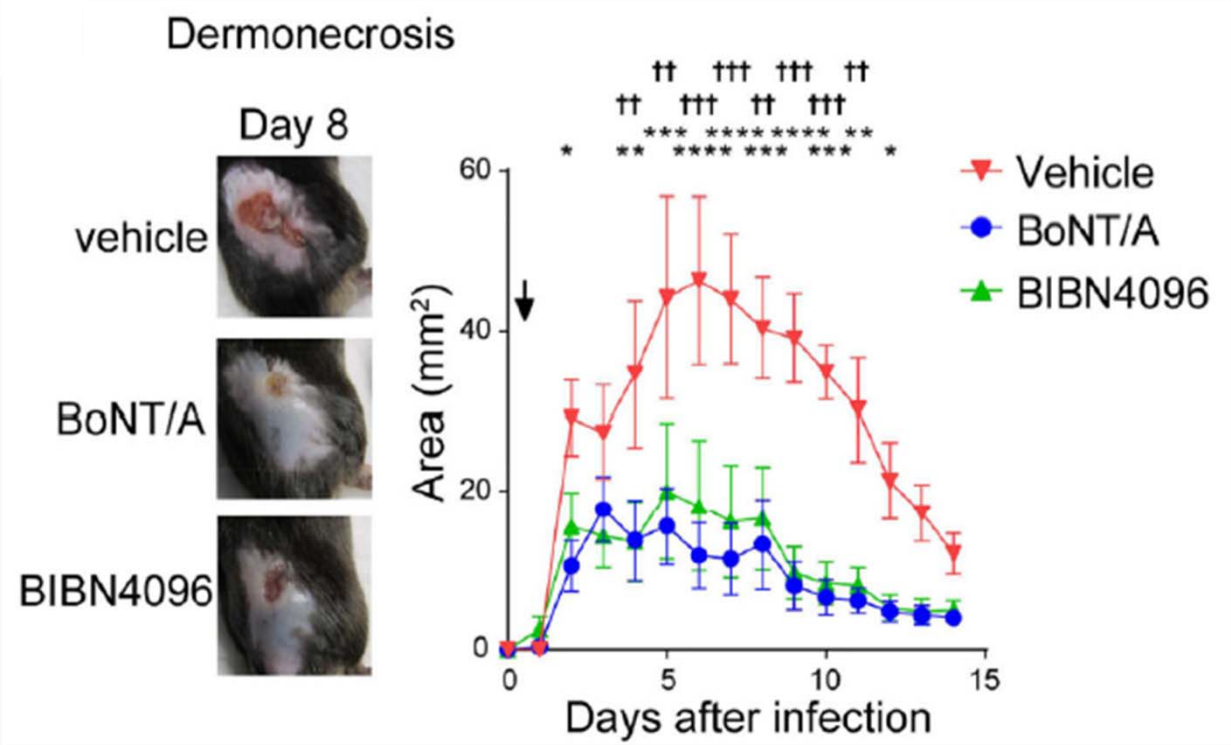
Nociceptor interact with immune system



- Nav1.8-Cre/diphtheria toxin A (DTA) mice: nociceptor deficient
- Larger lymph nodes and increased immune cells

(Chiu et al. *Nature*. 2013)

Possible target for treating bacterial invasion



Dermonecrosis size of mice treated with Streptococcus. pyogenes injection with vehicle or DRG neuron signaling inhibitors

- Blocking neuro-immune interaction is a promising strategy to treat highly invasive bacterial infections

(Pinho-Ribeiro et al. *Cell*. 2018)

Part 04

Conclusion

- Bacteria can directly modulate nociception distinct from immune defense
- Molecular elements from Bacteria can interact with nociceptors through different pathways
- Nociceptor targeting therapies could be used to treat bacteria infections

Reference

- Chiu IM, Heesters BA, Ghasemlou N, Von Hehn CA, Zhao F, Tran J, et al. Bacteria activate sensory neurons that modulate pain and inflammation. Nature. 2013; 501(7465):52–7.
- Pinho-Ribeiro FA, Baddal B, Haarsma R, O'Seaghdha M, Yang NJ, Blake KJ, et al. Blocking Neuronal Signaling to Immune Cells Treats Streptococcal Invasive Infection. Cell. 2018; 173(5):1083–97.
- Ruhl CR, Pasko BL, Khan HS, Kindt LM, Stamm CE, Franco LH, et al. Mycobacterium tuberculosis Sulfolipid-1 Activates Nociceptive Neurons and Induces Cough. Cell. 2020; 181(2):293–305
- Marion E, Song OR, Christophe T, Babonneau J, Fenistein D, Eyer J, et al. Mycobacterial toxin induces analgesia in buruli ulcer by targeting the angiotensin pathways. Cell. 2014; 157(7):1565–76.
- Deng L, Chiu IM. Microbes and pain. PLoS Pathog. 2021; 17(4): e1009398
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009; 139(2):267–84
- Basbaum, A.I., and Jessell, T. (2000). The perception of pain. In Principles of Neuroscience, E.R. Kandel, J. Schwartz, and T. Jessell, eds. (New York: Appleton and Lange), pp. 472–491.

Thank you for listening !