Context-Dependent Roles of Necroptotic Signalling in Cutaneous Inflammation

Implications for Atopic Dermatitis Pathogenesis and Therapeutic Targeting

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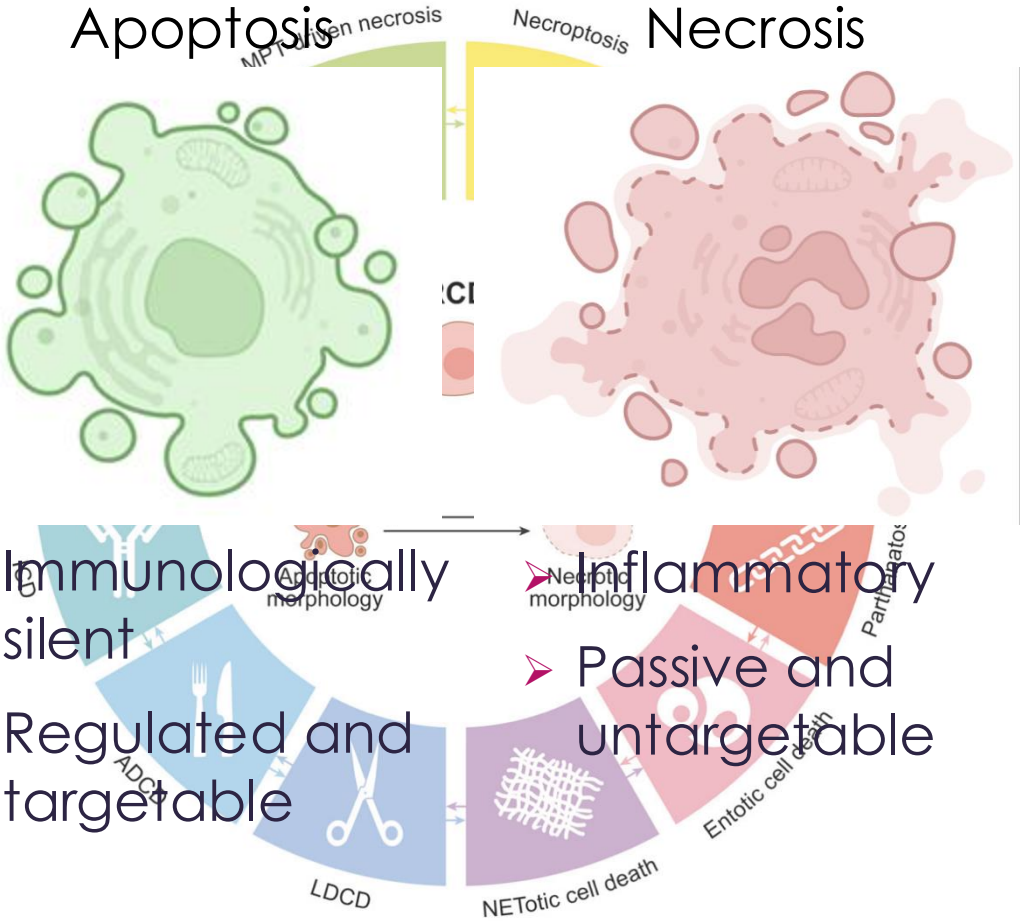
WEHI
brighter together

Programmed cell death as a driver of inflammation

The hidden stories of "necrotic" cells

Galluzzi et al, 2018, CD&D

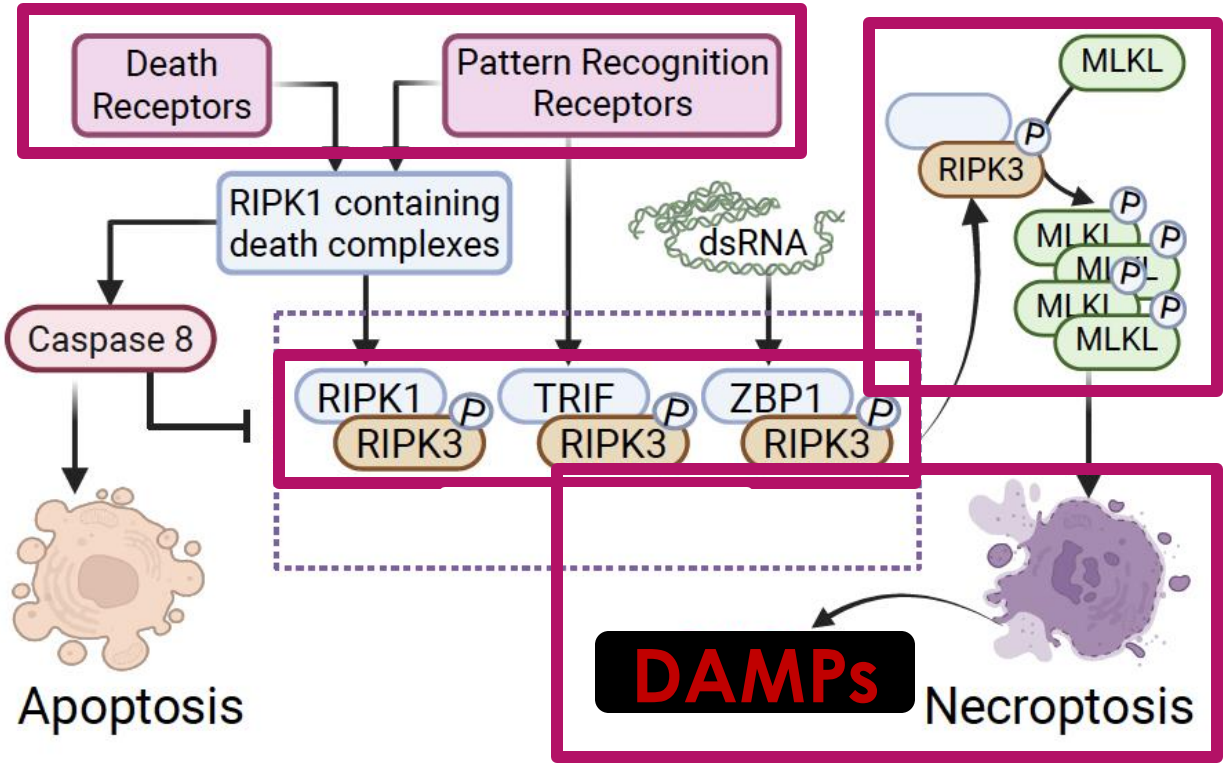


- Immunologically silent
- Regulated and targetable

- Inflammatory
- Passive and untargetable

Necroptosis

Pro-inflammatory programmed cell death



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Necroptosis deficiency accelerates cutaneous recovery

- In three skin disease models
  - Smac-mimetic induced TEN
  - Induced loss of cFlip in the skin
  - Excision wounds

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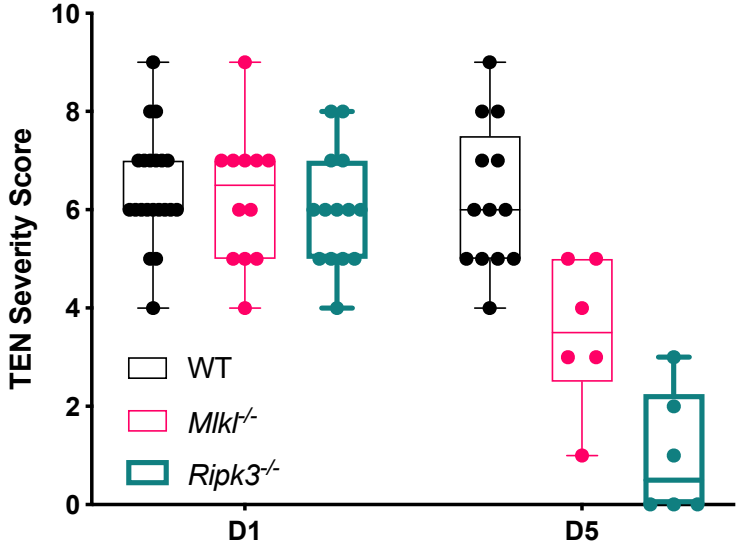
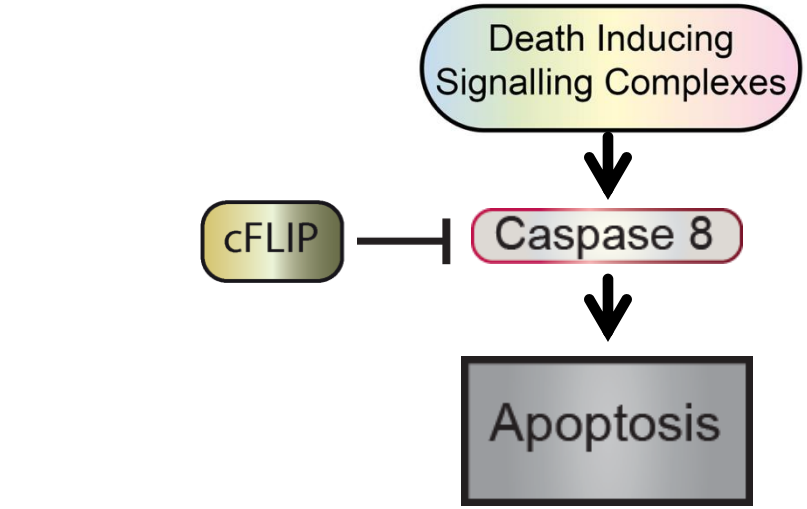
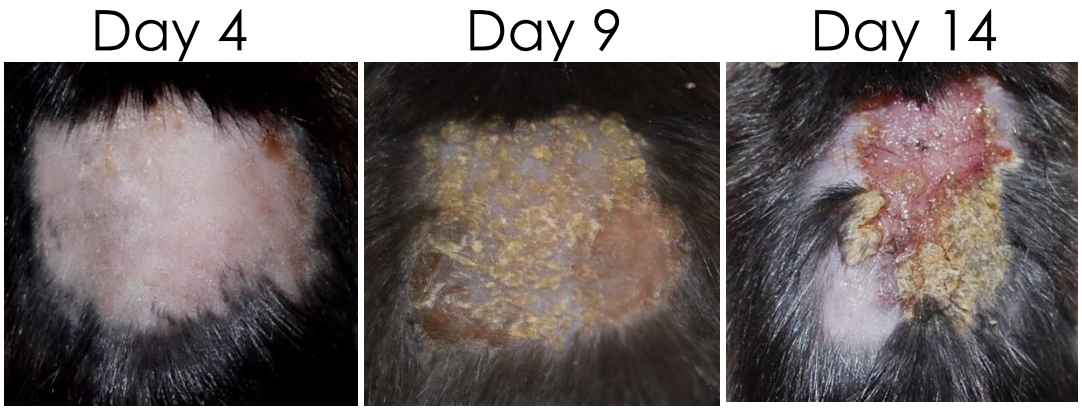
- Necroptotic KOs recover faster in 3 models of cutaneous injury
  - SM induced TEN

SM induced Lesions Day 5



- Necroptotic KOs recover faster in 3 models of cutaneous injury
  - SM induced TEN
  - Tamoxifen induced loss of cFLIP





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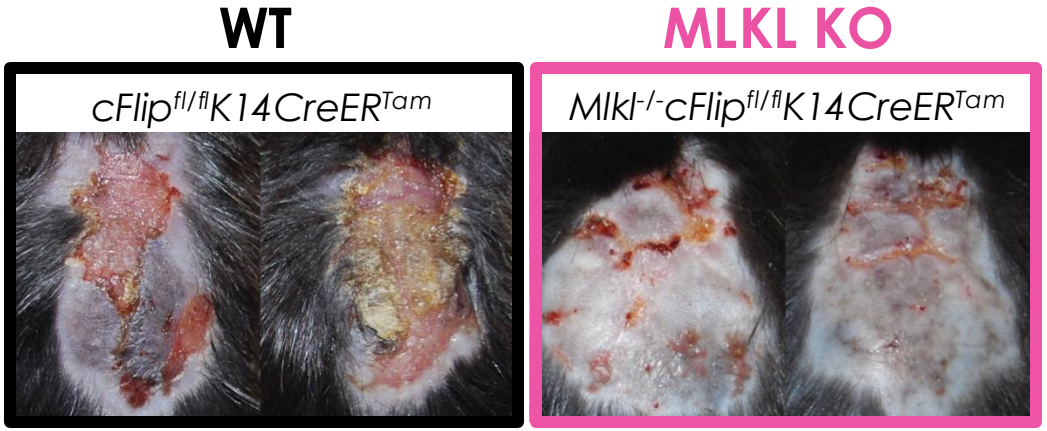
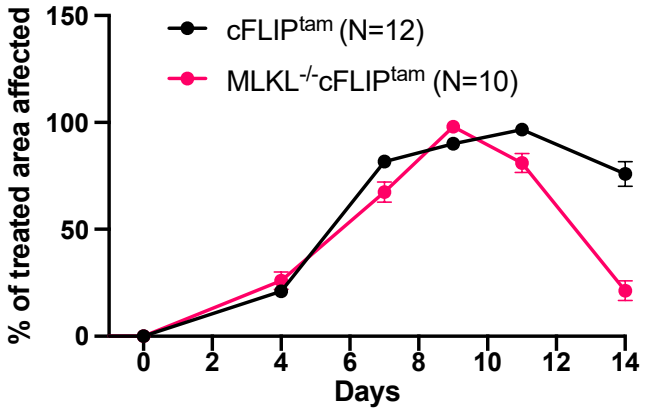
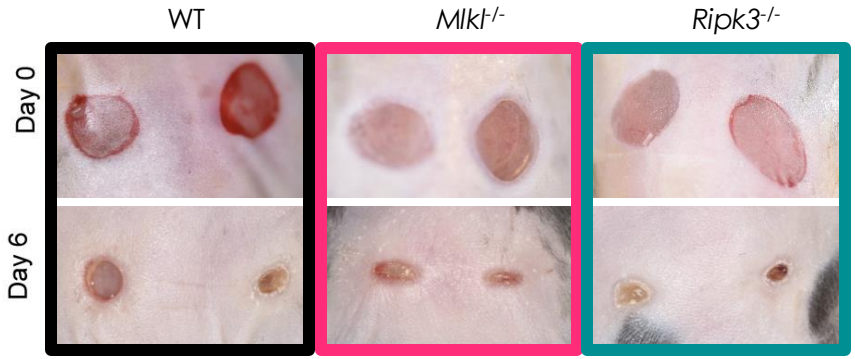
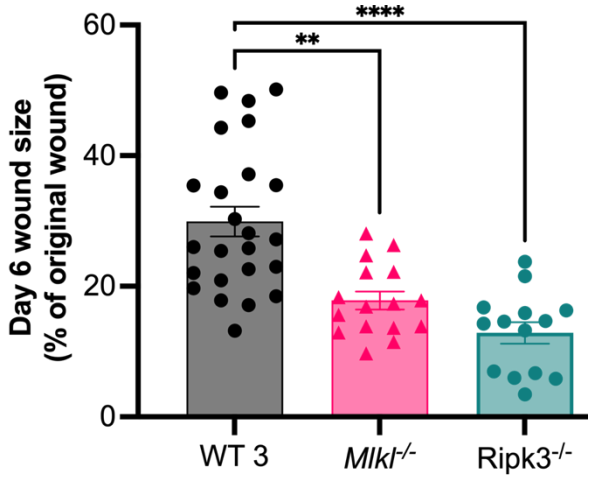
Day 14





- Necroptotic KOs recover faster in 3 models of cutaneous injury
  - SM induced TEN
  - Tamoxifen induced loss of cFLIP
  - Full thickness excision wounds





Necroptosis deficiency accelerates cutaneous recovery

- In three skin disease models
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  - Induced loss of cFlip in the skin
  - Excision wounds

Necroptosis = Bad

Full thickness excision wounds

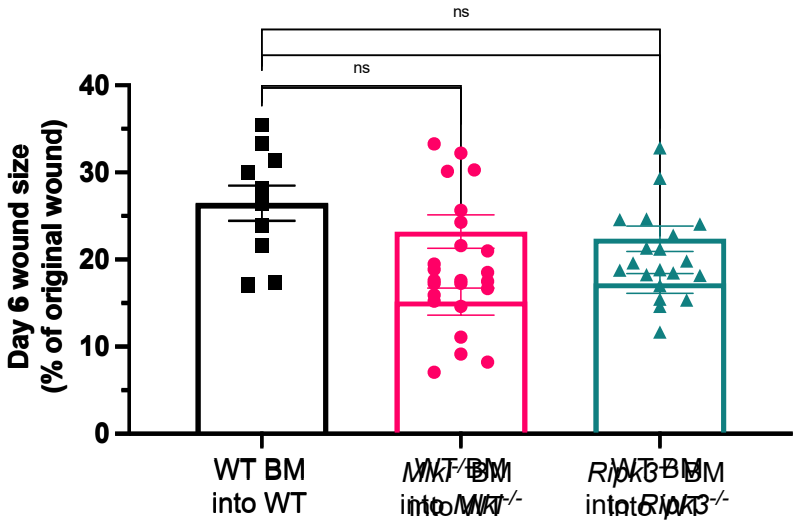
WTs with Nec BM

no healing advantage

Nec KOs with WT BM

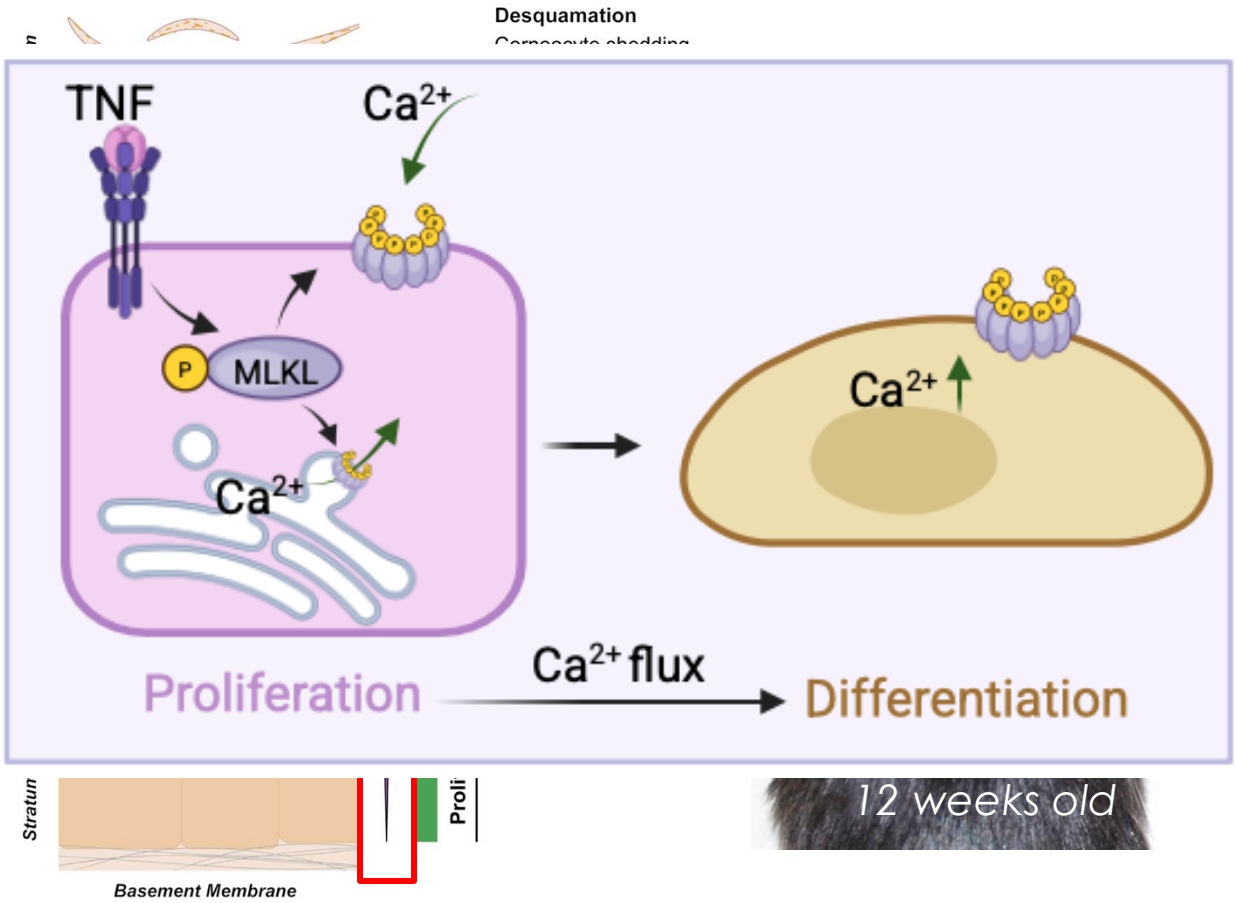
retain the healing advantage

Relative wound recovery at day 6



Hypothesis

Activated MLKL creates pores in the cell membrane that enable calcium flux triggering terminal differentiation rather than necroptotic cell death



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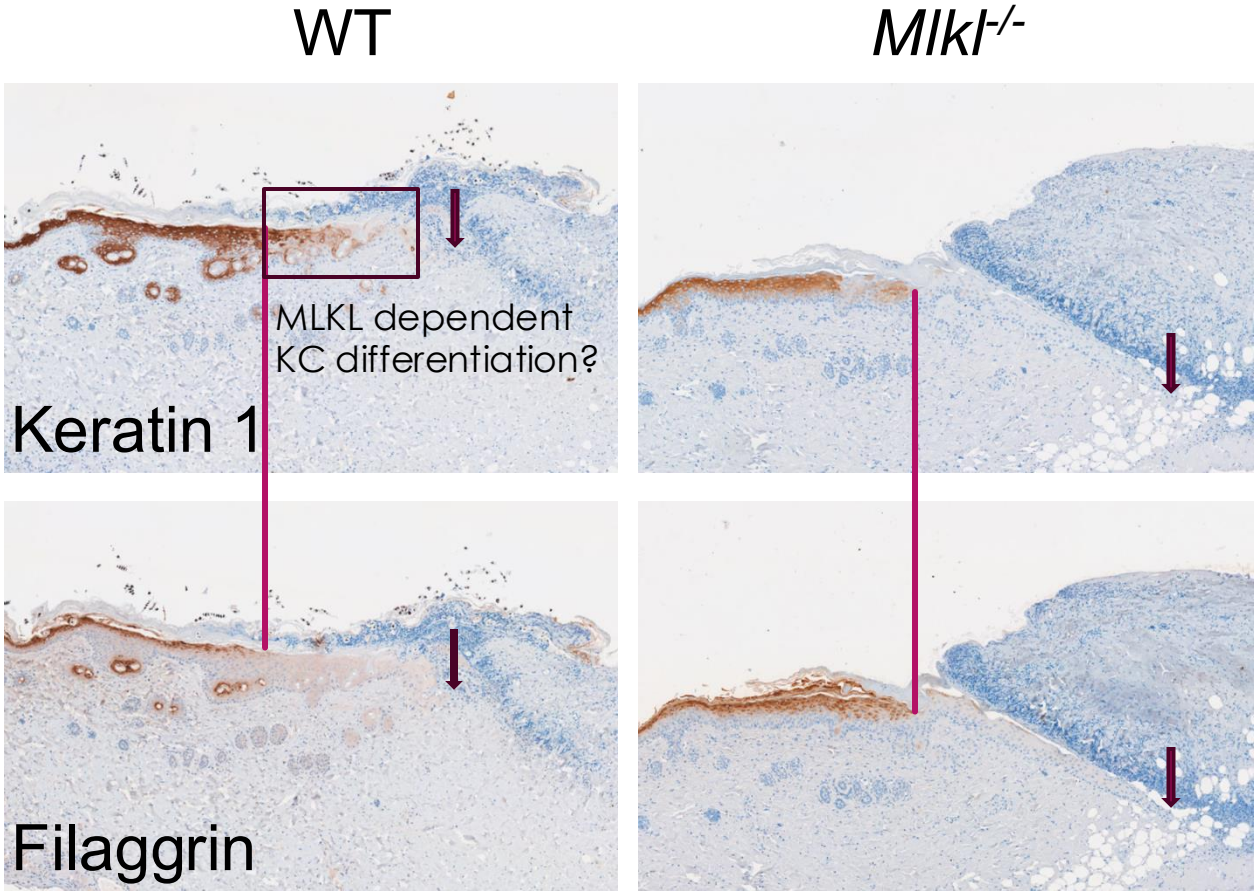
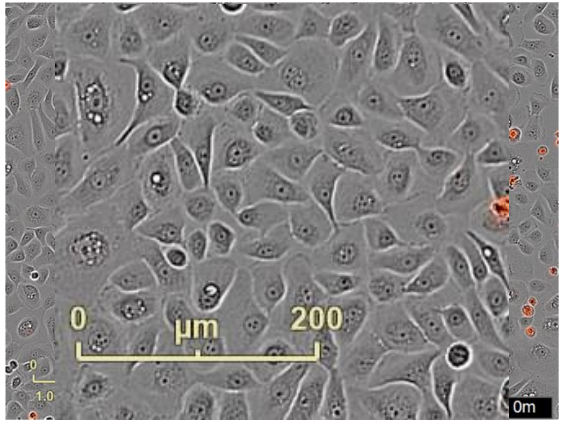
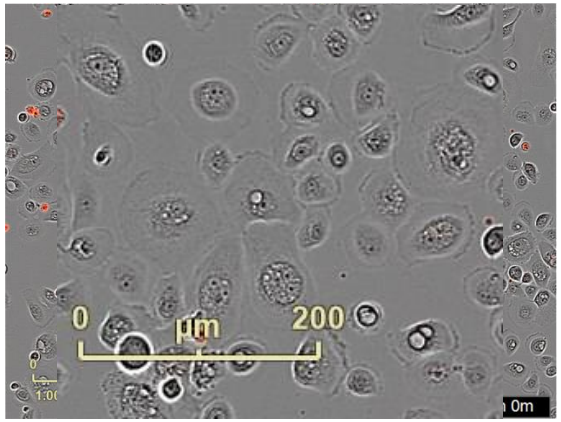
Early marker of differentiation occurs closer to healing fronts in WT skin

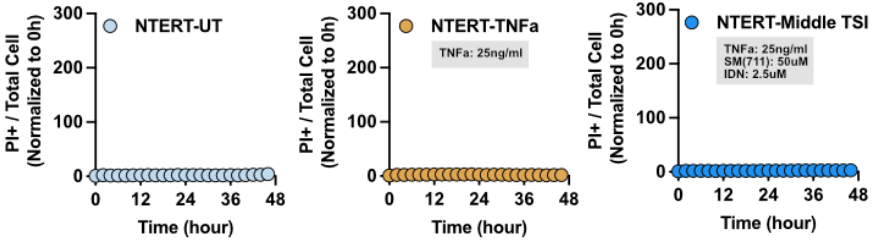


Sub-lethal Necroptosis induces differentiation in cultured human keratinocytes

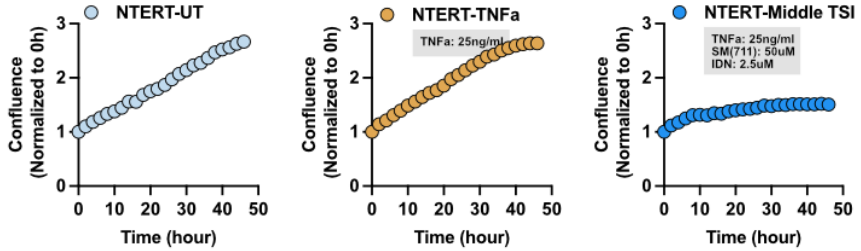




Cell Death (red is dead)

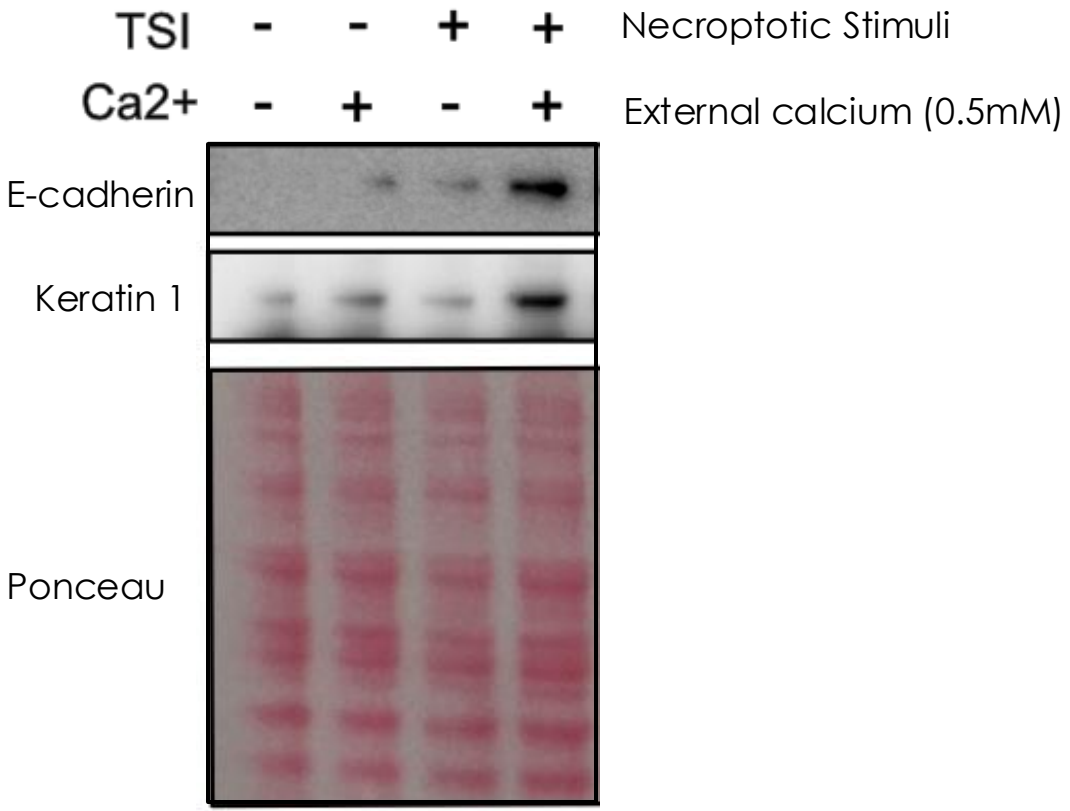


Confluence (proliferation)



Yingxue He (PhD student) and Gu Lok Hei (InSpire student)

Sub-lethal Necroptosis induces differentiation in cultured human keratinocytes



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But wait….

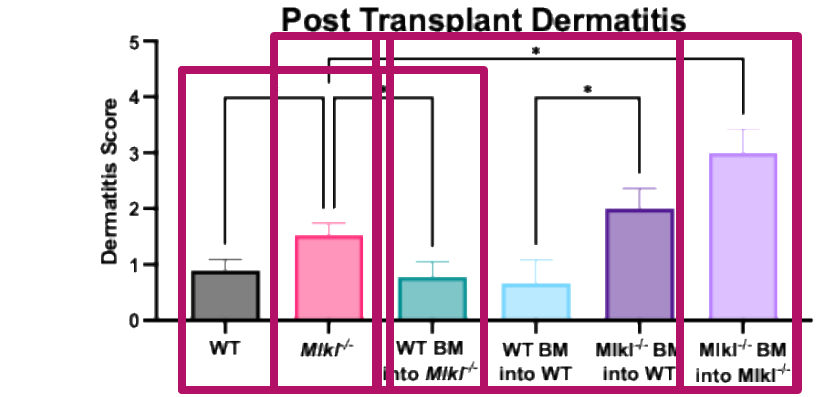
Dressing-associated dermatitis

Necroptosis = Bad

Necroptotic signalling in keratinocytes slows healing but…

- not simply necroptosis -> cell lysis -> inflammation
- Instead necroptosis-> differentiation -> reduced proliferation & migration

Immune cell necroptotic signalling limits cutaneous over-reactions



Necroptosis = Good?

Divergent Roles of Necroptosis in Skin Inflammation and Barrier Disruption

Necroptosis = Bad *and* Good

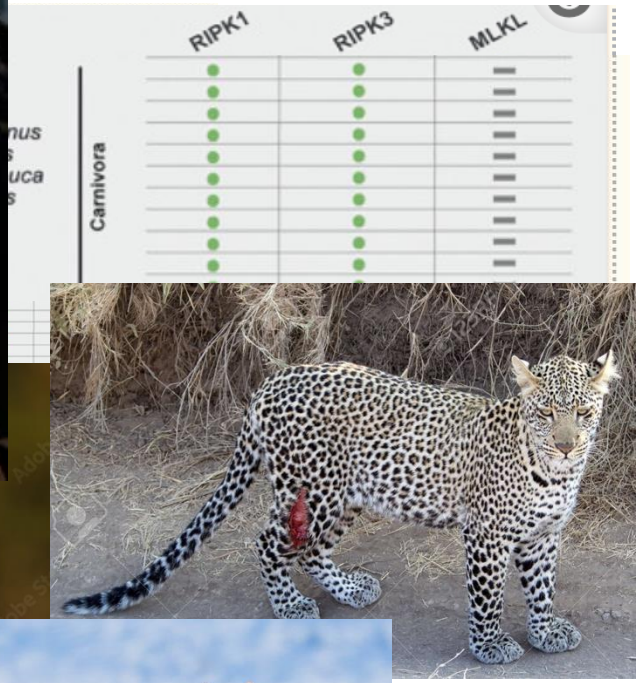
Loss of necroptosis in the skin enhances recovery from epidermal barrier disruption.

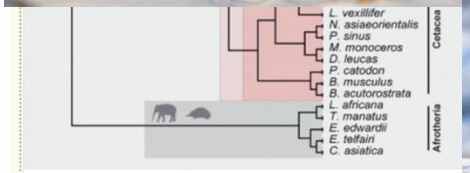
Loss in immune cells sensitises to cutaneous over-reactions

Effect is massively amplified post-BMT

Convergent evolution - loss of necroptosis function in mammals

- Loss of necroptosis is baseline non-pathogenic
- May be advantageous in some situations – see carnivores and wound healing
- May become pathologically significant when combined with other risk factors





Ana Águeda-Pinto, Front Immunol. 2021

Clinical and therapeutic implications

Loss of necroptosis in the skin enhances recovery from epidermal injury

- Target to treat wounds, burns, barrier disruption disorders

Loss in immune cells sensitises to cutaneous over-reactions

- Pan-inhibition of necroptosis could backfire
- Is necroptosis deficiency a risk factor in AD?
- Necroptotsis deficient BMT donors as a risk factor.

Loss of necroptosis in the skin enhances recovery from epidermal injury

Loss in immune cells sensitises to cutaneous over-reactions

THANKS!

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