Sterile and non-sterile inflammation of the skin
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Sterile and non-sterile inflammation of the skin
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Allergic Contact Dermatitis to the preservative Kathon CG (MCI/MI)

methylchloroisothiazolinone and methylisothiazolinone

“We are in the midst of an outbreak of allergy to a preservative (MI) which we have not seen before in terms of scale in our lifetime“
Dr John McFadden
Allergic and irritant contact dermatitis – no T cell response without innate immune response

- Allergic contact dermatitis
- Irritant contact dermatitis

Tissue stress/damage → danger signals: ROS, DAMPs etc. → innate immune cells: mast cells, neutrophils etc. → sterile skin inflammation (xenoinflammation)

Contact allergen → T cell priming → P2X7R, NLRP3, TLR2/4, MHC/hapten/peptide → DC activation, migration

Innate immune response

Contact irritant → allergic contact dermatitis

Prof. Dr. P. Altmeyer
Orchestration of the innate cellular immune response to contact allergens
Innate cellular players in the mouse dermis
(skin wounding model, Lämmermann/Germain)

mast cells (blue), neutrophils (red)
macrophages and dendritic cells (yellow)
lymphatic vessels, blood vessels, fat cells (white)
The mouse **Contact HyperSensitivity (CHS) model**

*(Mouse Ear Swelling Test (MEST))*

> sensitization by abdominal painting

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**day 0:** sensitization

3% TNCB

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**day 5:** elicitation

1% TNCB, ears

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**day 5, 6:** measurement of ear swelling
Mast cells are required for CHS

MC deficient mice

MC depletion before sensitization

Role of neutrophils in contact hypersensitivity

Neutrophil depletion before sensitization or before elicitation prevents CHS

Orchestration of skin inflammation by innate immune cell-crosstalk

contact allergen

danger signals: ROS, DAMPs etc.

mast cell activation

DC activation, migration

neutrophil recruitment and activation

T cell priming

Orchestration of the innate molecular immune response by contact allergens
Non-sterile skin inflammation: *danger signals* activate the innate immune system and thereby trigger inflammation.

TLR4, TLR2, LPS, lipopeptide, NLRP3, ASC, caspase-1

- Toll-like receptors
- NLRP3 inflammasome
- Activation of the innate immune system
- Inflammation: DC activation and migration

TLR, NLRP3 etc.: Pattern Recognition Receptors (PRR, Charles A. Janeway)
Species-specific differences in allergic contact dermatitis: LPS, a ligand for TLR4, provides the missing innate danger signal

- **Mouse**
  - Ni$^{2+}$
  - Ni$^{2+}$ + LPS
  - no CHS
  - normal CHS

- **Man**
  - Ni$^{2+}$
  - normal CHS

Ni$^{2+}$
Nickel and cobalt bind directly to human but not mouse TLR4 and induce receptor dimerization

Resistance to TNCB, oxazolone and FITC induced CHS in TLR2/TLR4 double deficient mice

- no direct TLR modification
- CHS works in germ-free mice !!!
⇒ no role for PAMPs/MAMPs
⇒ need for endogenous danger signals

Indirect triggering of TLR2/4 by contact allergen-induced formation of endogenous ligands in the skin – breakdown of hyaluronic acid (HA)

 limitation of *in vitro* assays!

Indirect and direct activation of innate signalling pathways by contact allergens


Martin S.F. Contact Dermatitis 72:2-10 (2015)
Innate immune responses to contact allergens and potential anti-inflammatory treatment strategies

or

“For the mice in the audience, I have wonderful news!”

from Stanford Med., The Bodyguard, Summer 2011, Bruce Davis

<table>
<thead>
<tr>
<th>Role</th>
<th>TNCB, Oxa etc.</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role for TLR (cell type)</td>
<td>TLR2, TLR4 (DC)</td>
<td>TLR antagonists/mAbs</td>
</tr>
<tr>
<td>Activating DAMP (source)</td>
<td>hyaluronic acid fragments (ECM)</td>
<td>HAdase inhibitors</td>
</tr>
<tr>
<td>Role for ROS</td>
<td>+</td>
<td>antioxidants</td>
</tr>
<tr>
<td>Role for P2X7R (cell type)</td>
<td>+ (DC)</td>
<td>P2X7R antagonists (KN-62 etc.)</td>
</tr>
<tr>
<td>Role for NLRP3 inflammasome (cell type)</td>
<td>+ (DC)</td>
<td>inhibitors (glyburide, aspirin etc.)</td>
</tr>
<tr>
<td>Role for IL-1β</td>
<td>+</td>
<td>IL-1R antagonists/mAbs (Anakinra etc.)</td>
</tr>
</tbody>
</table>

DC: dendritic cell
ECM: extracellular matrix

marked in red: works in the CHS model (our data)
Innate immune response to acetaminophen (APAP) in drug-induced liver injury (DILI)


Martin S.F. *Contact Dermatitis* 72:2-10 (2015)
Orchestration of skin inflammation by innate immune and cellular stress responses

contact allergens (TNCB, oxazolone etc.)

activation of the innate immune system

activation of cellular stress responses

skin inflammation
Summary

• Contact allergens trigger mast-cell dependent neutrophil recruitment to the skin
• Interplay between mast cells, neutrophils, dendritic cells etc. essential for the orchestration of the cellular innate immune response
• Contact allergens trigger TLR- and NLRP3-dependent inflammatory pathways
• Endogenous danger signals (HA fragments, ROS, ATP) play an essential role
• Interplay between these innate signaling pathways essential for the orchestration of the molecular innate immune response

⇒ Elimination/inhibition of one element can prevent sensitization/CHS
⇒ A critical threshold cannot be reached

• Tissue stress and damage responses are essential elements of skin inflammation

⇒ Mechanistic understanding of adverse reactions to chemicals essential to improve diagnostics, treatment and hazard identification
Thank you!

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