Common clonal origin of central and resident memory T cells following skin immunization

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Introduction

T-Cell Activation and Diversity

Introduction

Memory T cell subsets

Introduction

Circulation of Memory T cell subsets

- Remain at tissue only
- Scan for Antigen everywhere
- Remain in lymph and blood
- Scan for new antigen

*Immunity* 41, 886–897 (2014)
Introduction

Central memory T cell ($T_{CM}$)

- CCR7
- CD62L (L-selectin, vascular addressin)
- Limited effector function or protective capacity
- Ability to replenish $T_{RM}$ compartment upon activation

Effector memory T cell ($T_{EM}$)

- Low expression of CCR7 and CD62L
- CLA (E-selectin ligand), CCR4, CCR8, CCR10 $\rightarrow$ skin homing
- $\alpha 4\beta 7$, CCR9 $\rightarrow$ gut homing

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Introduction

Tissue-resident memory T cells ($T_{RM}$)

- Reside in epithelial barrier tissue
  - gastrointestinal tract (GI)
  - respiratory tract
  - reproductive tract
  - skin

Introduction

Tissue-resident memory T cells (T_{RM})

- CD69^+ (involved in tissue retention)
- Mostly CD103^+
- Sphingosine 1 phosphate receptor (S1P1)↓
- Kruppel-like factor 2 (KLF-2)↓

Tissue-resident memory T cells ($T_{RM}$) in tissue-specific autoimmune and inflammatory diseases

Aim/Questions addressed

- The investigation of the clonal origin of $T_{CM}$ and $T_{RM}$
- Effect on abundance of $T_{RM}$ after repetitive sensitization
- Differences in kinetics between allergen-specific $T_{CM}$ and $T_{RM}$
- Generation of $T_{RM}$ due to DPCP induced ACD
Methods

High-throughput sequencing (HTS) of T cell receptor (TCR) β-chain (TRB)

- **CDR3** sequence (part of variable region, highly specific)
- Possibility to track thousands of unique T cells

*Nat. Med. 21, 688–697 (2015)*

http://www.irepertoire.com/the-immune-repertoire
Methods

Antigen challenge to skin

- Ovalbumin (OVA) + adjuvant cholera toxin (CT)
- Dinitrofluorobenzene (DNFB)
- Modified Vaccinia Ankara (MVA)

Methods

Antigen challenge to skin

- Fingolimod (FTY720) T cell retention

*Figure 1* Mechanism of action of FTY720


Methods

Parabiotic surgery

- Sex- and age-matched mice
- Connection of a sensitized mouse to a naive mouse
- Common blood circulation
- Separation after 4 weeks

Nat. Med. 21, 688-697 (2015)
Methods

Study subjects and skin samples

- 11 healthy volunteers
- Diphenylcyclopropenone (DPCP) immunization and challenging → allergic contact dermatitis (ADC)
- Skin biopsies (day 4, 13 and month 4)
Results

Skin immunization with $\text{OVA} + \text{CT}$ generates skin $\text{T}_{\text{RM}}$ cells and TCR-identical $\text{T}_{\text{CM}}$ cells in LNs.

$I =$ inguinal LN  
$T =$ tail skin  
$E =$ ear skin  
$D =$ draining LN (ear draining)

Results

Skin immunization with DNFB generates skin $T_{RM}$ cells and TCR-identical $T_{CM}$ cells in LN.

$I = \text{inguinal LN}$
$T = \text{tail skin}$
$E = \text{ear skin}$
$D = \text{draining LN (ear draining)}$

Results

Skin immunization with MVA generates skin $T_{RM}$ cells and TCR-identical $T_{CM}$ cells in LNs

I = inguinal LN
T = tail skin
E = ear skin
D = draining LN (ear draining)

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Results

Repetitive sensitization increases the abundance of T\textsubscript{RM} cells in skin

**Results**

Repetitive sensitization increases the abundance of $T_{RM}$ cells in skin

<table>
<thead>
<tr>
<th>Mouse</th>
<th>0 exposures (tail)</th>
<th>2 exposures (right ear)</th>
<th>6 exposures (left ear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse 1</td>
<td>26</td>
<td>114</td>
<td>381 (36 in LN)</td>
</tr>
<tr>
<td>Mouse 2</td>
<td>52</td>
<td>229</td>
<td>406 (60 in LN)</td>
</tr>
<tr>
<td>Mouse 3</td>
<td>62</td>
<td>220</td>
<td>256 (15 in LN)</td>
</tr>
</tbody>
</table>

**f:**

- No. of expanded clones ($>10$ cells)
  - Mouse 1: 18 (16 in LN)
  - Mouse 2: 30 (13 in LN)
  - Mouse 3: 2 (2 in LN)

Results

\(T_{RM}\) cells mediate rapid skin contact hypersensitivity (CHS) responses, whereas \(T_{CM}\) cells mediate delayed attenuated CHS responses.

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Results

Contact dermatitis to DPCP induces $T_{RM}$ cells in human skin.

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Summary

• Skin immunization with different antigens generates skin $T_{RM}$ cells and TCR-identical $T_{CM}$ cells in LNs.

• Repetitive sensitization increases the abundance of $T_{RM}$ cells in skin.

• $T_{RM}$ cells mediate rapid skin contact hypersensitivity (CHS) responses, whereas $T_{CM}$ cells mediate delayed attenuated CHS responses.

• Contact dermatitis to DPCP induces $T_{RM}$ cells in human skin.

Conclusion

• Allergic contact dermatitis (ACD) mediation by $T_{RM}$ explains recurrent and site-specific nature of disease.

• TCR-identical $T_{RM}$ (peripheral tissue) and $T_{CM}$ (LN) $\rightarrow$ two compartments of memory T cells with identical TCR but different effector properties.

• Human diseases that recur episodically in barrier tissue may be mediated by $T_{RM}$. 
Thank you for your attention