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Tissue Resident Memory T Cells (T_{RM})

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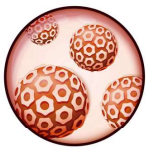
1

CD8 T cells

Provide protection against infections by intracellular pathogens



Viruses

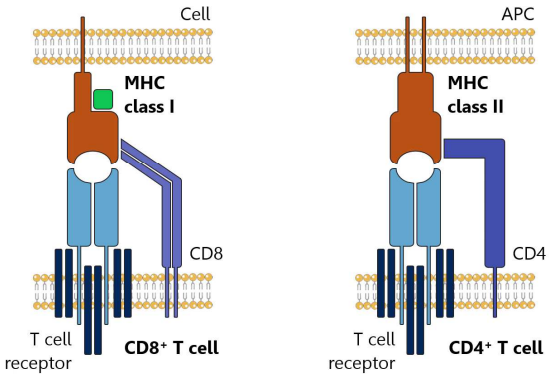
Protozoan parasites

Bacteria

Provide protection against **tumours**

2

Two main T cell subsets



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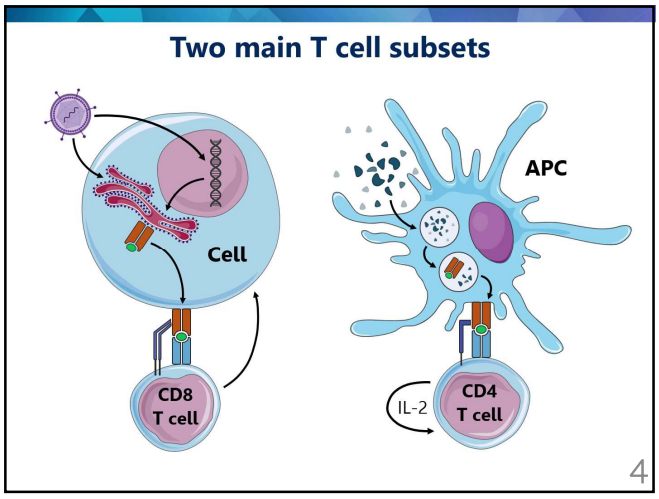

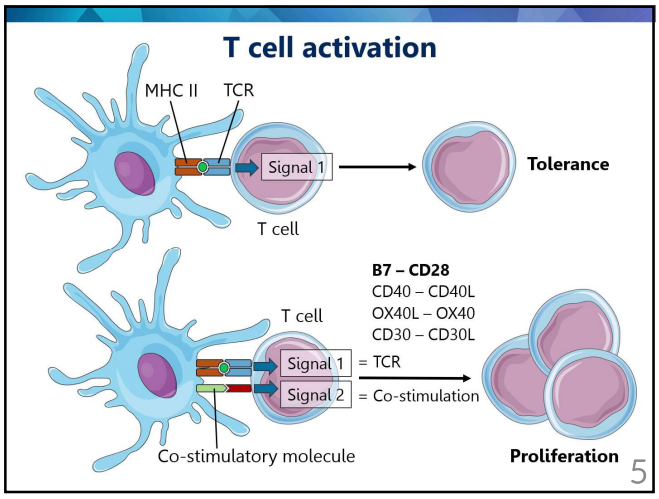

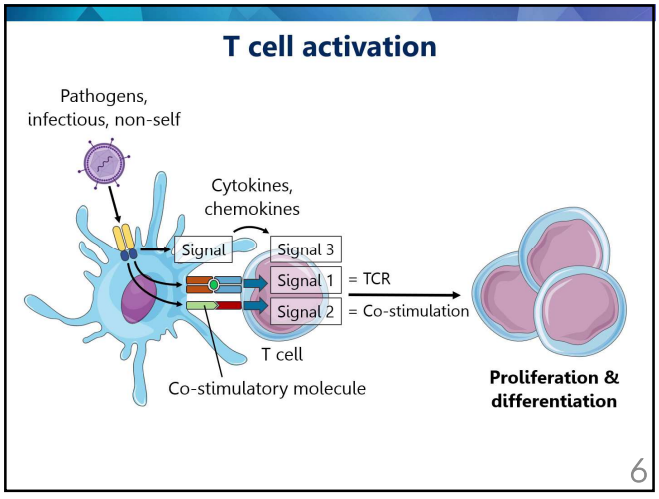

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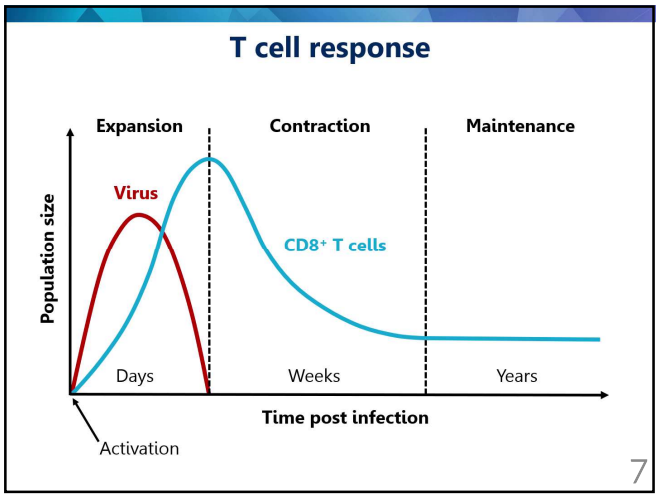

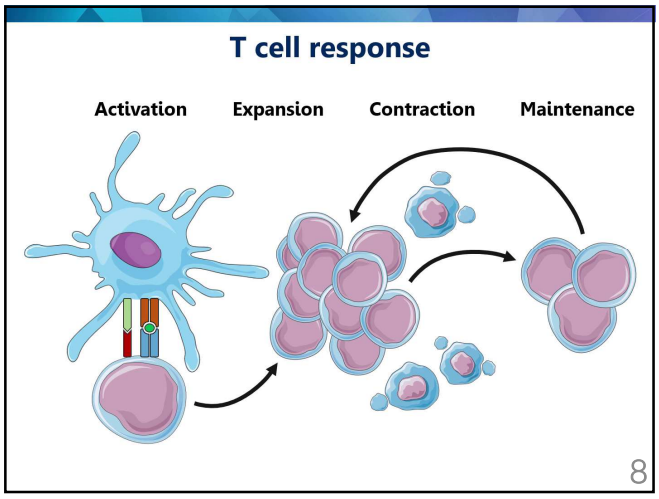

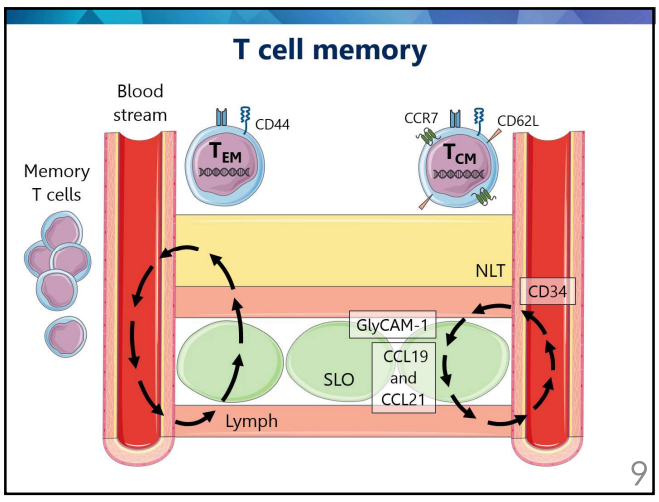

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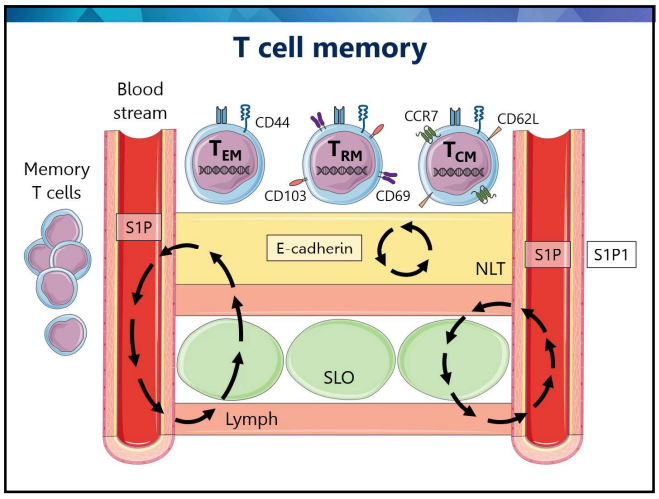

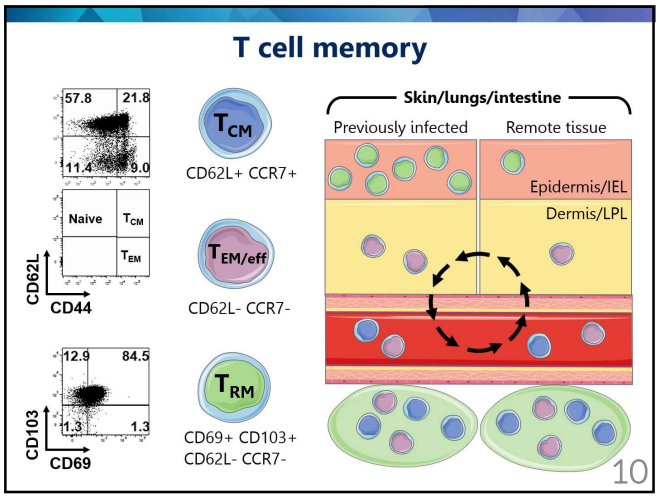

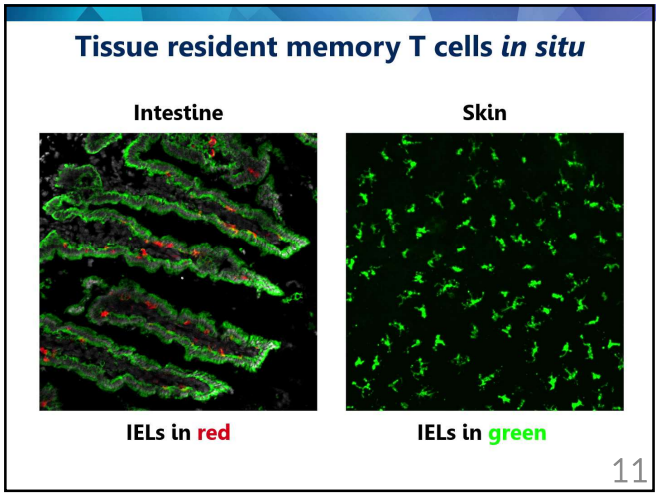

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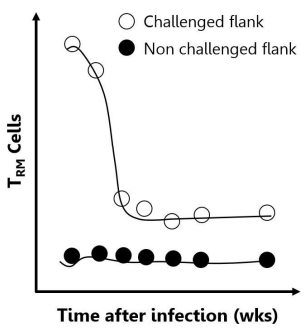
T cell memory persists in skin after infection



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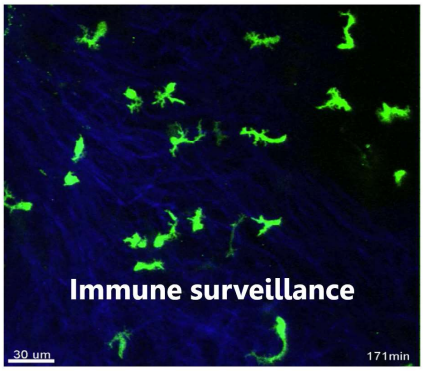
Experimental data e.g., Gebhardt T. *et al, Nat Immunol.* 2009; **10**(5):524-30

T_{RM} cells scan the epithelial barrier after infection has been cleared



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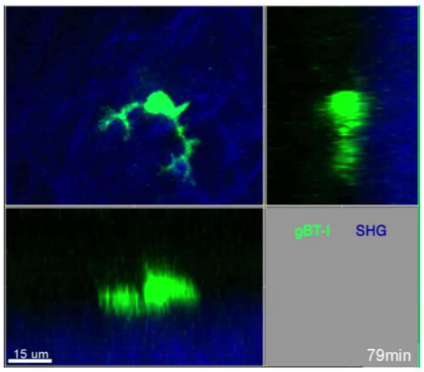
T_{RM} scan only within their tissue compartment



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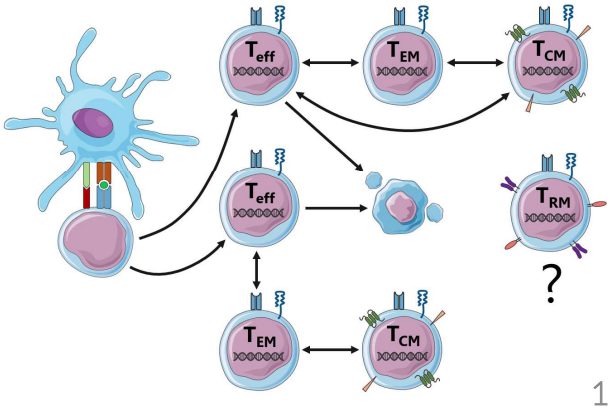
How do T_{RM} cells develop?



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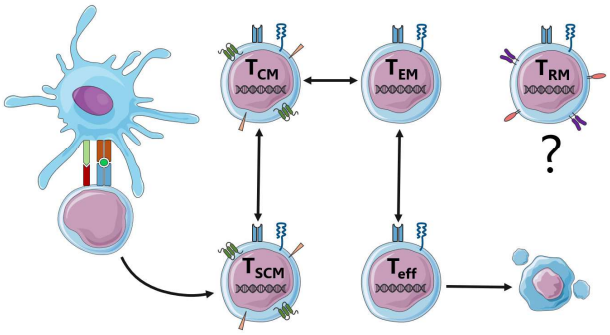
How do T_{RM} cells develop?



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Summary

	Cell surface	Transcription factors	Location
T_{EM}	CCR7- CD62L- CD69- CD103-	$Tbet^{hi}$ $Eomes^{hi}$ AhR-	SLO + NLT
T_{CM}	CCR7+ CD62L+ CD69- CD103-	$Tbet^{lo}$ $Eomes^{hi}$ AhR-	SLO
T_{RM}	CCR7- CD62L- CD69+ CD103+	$Tbet^{lo}$ Eomes- AhR+	NLT

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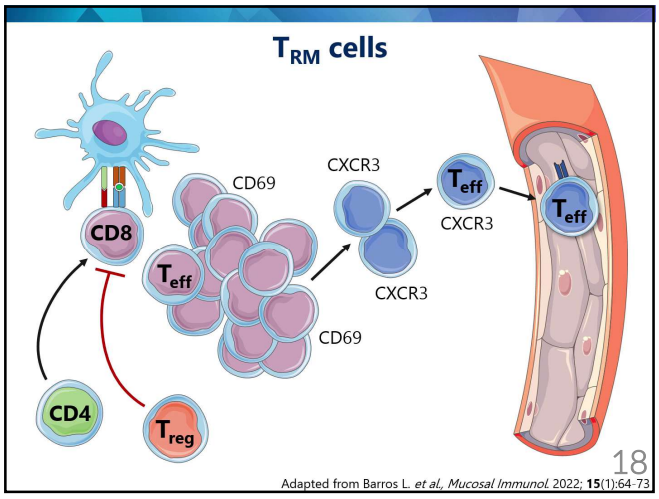

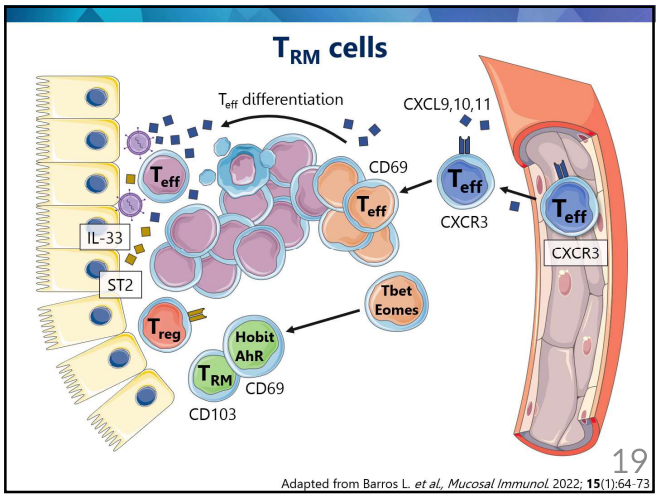

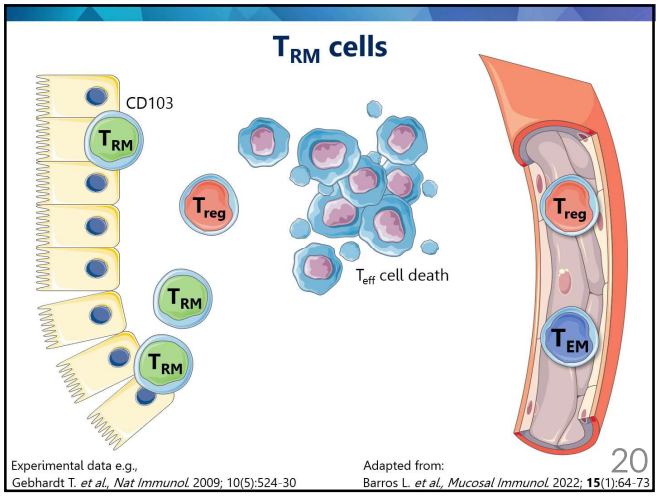

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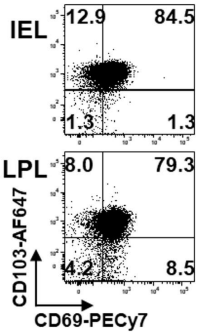
T_{RM} cell transcription factors

- Requirement for formation and maintenance are IL-15 and TGFβ
- T_{RM} have a unique transcriptional profile
  - Expression of the transcription factors Hobit, Blimp-1 and AhR
  - Limited, but required expression of Tbet (Tbx21)
  - Down regulation of Eomes
- This happens in all organs, with similar transcriptional profiles, but with organs specific differences



Experimental data e.g.,
Mackay L. *et al., Science.* 2016; **352**(6284):459-63

Mackay L. *et al., Nat Immunol.* 2013; **14**(12):1294-301

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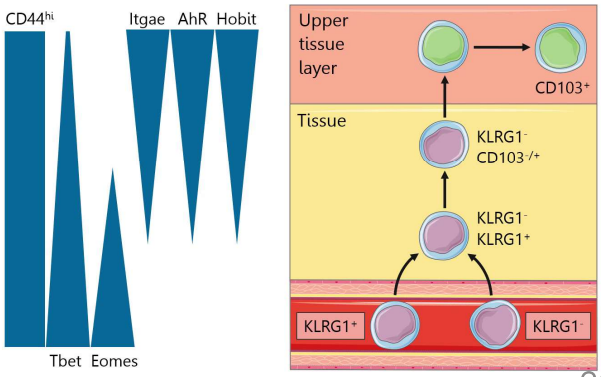
T_{RM} cell transcription factors



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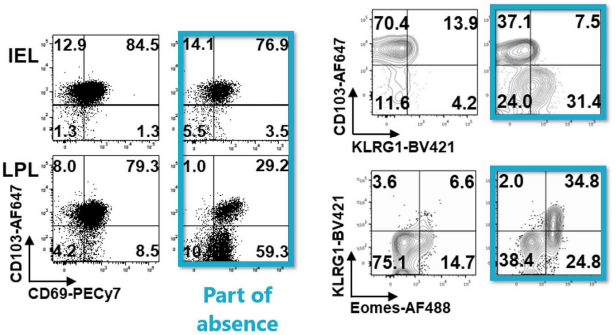
T_{RM} cell development



Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

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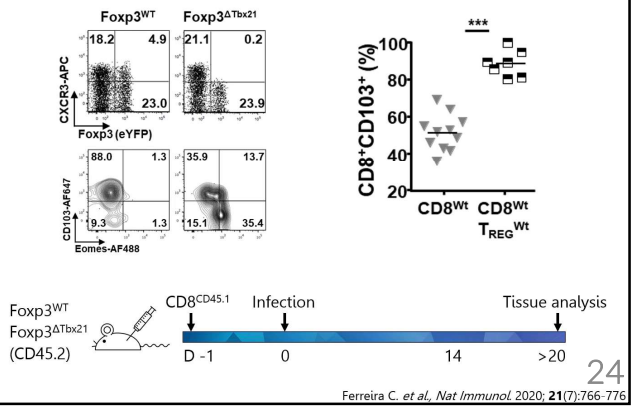
T_{RM} cell development



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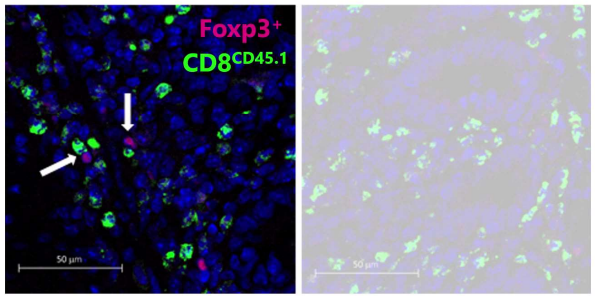
Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

T_{RM} cell development

Foxp3WT Foxp3ΔTbx21



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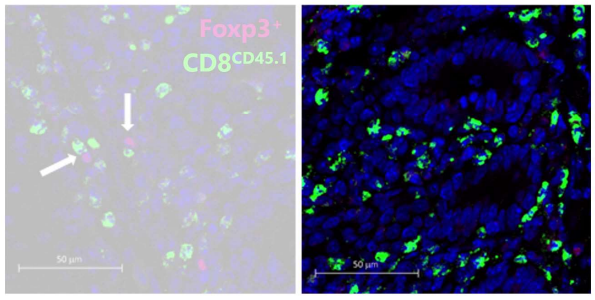
Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

T_{RM} cell development

Foxp3WT **Foxp3ΔTbx21**



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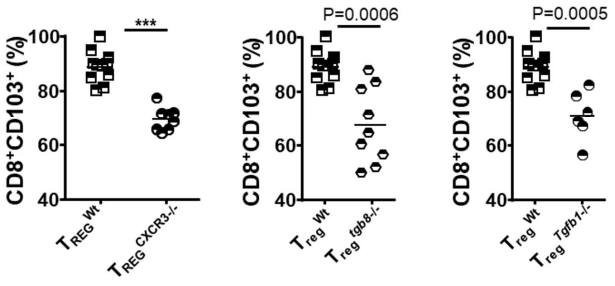
T_{RM} cell development



Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

T_{RM} cell function: model systems

- Tissue specific pathogen
- Intracellular parasite
- Natural mouse parasite
- *E. vermiformis* – small Intestine
- Self-limiting

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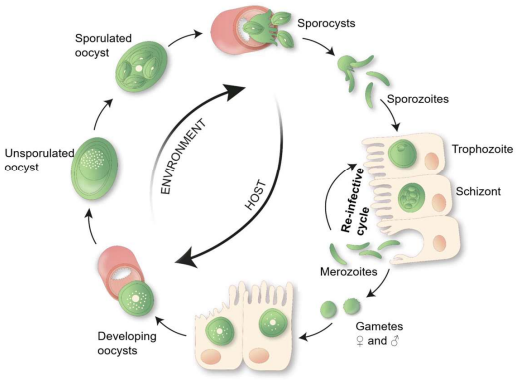
Figueiredo-Campos P. *et al., Bio Protoc.* 2018; **8**(24):e3122

T_{RM} cell function: model systems



Figueiredo-Campos P. *et al., Bio Protoc.* 2018; **8**(24):e3122

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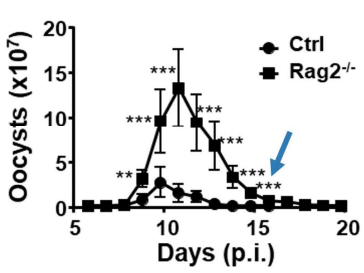
T_{RM} cell function



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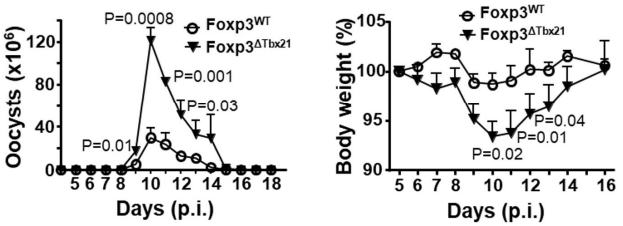
Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

T_{RM} cell function



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Ferreira C. *et al., Nat Immunol.* 2020; **21**(7):766-776

Memory CD8⁺ T cells protect against malaria

Article

Immunity

Liver-Resident Memory CD8⁺ T Cells Form a Front-Line Defense against Malaria Liver-Stage Infection

Fernandez-Ruiz D. *et al., Immunity.* 2016; 45(4):889-902

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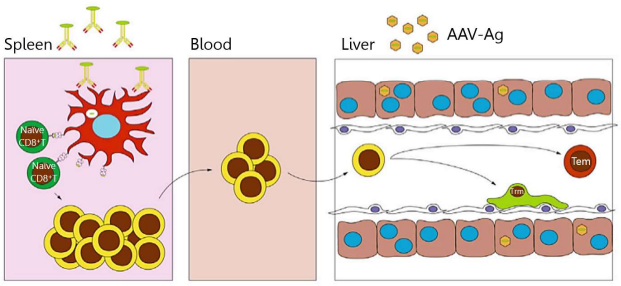
Memory CD8⁺ T cells protect against malaria

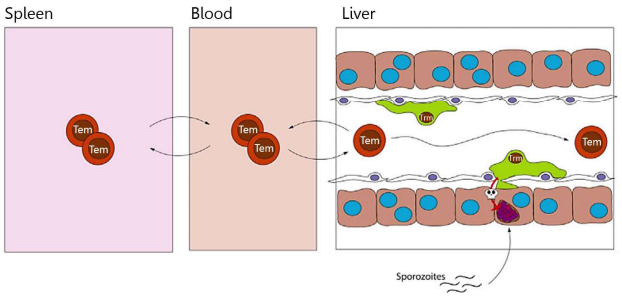
1. Anti-Clec9A antibodies target malaria antigen to CD8⁺ DC **"Prime"**

2. Liver infection with adeno-associated virus expressing malaria antigen drives liver-resident memory T cell formation **"Trap"**



Memory CD8⁺ T cells protect against malaria

Tissue-resident memory T cells kill malaria parasites in the liver

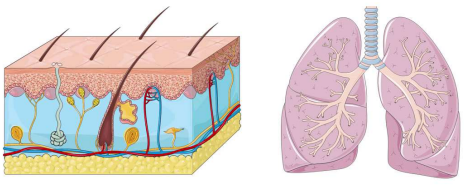


T_{RM} cell function

nature COMMUNICATIONS

RSV-specific airway resident memory CD8 + T cells and differential disease severity after experimental human infection

Jozwik A. *et al., Nat Commun.* 2015; 6:10224



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T_{RM} cell function

nature COMMUNICATIONS

RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection

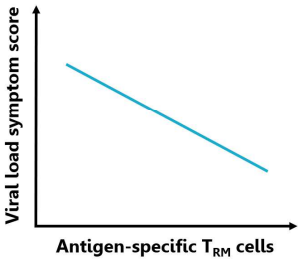
Jozwik A. *et al., Nat Commun.* 2015; 6:10224

Science Immunology

Resident memory CD8⁺ T cells in the upper respiratory tract prevent pulmonary influenza virus infection

Pizzolla A. *et al., Sci Immunol.* 2017; 2(12):eaam6970

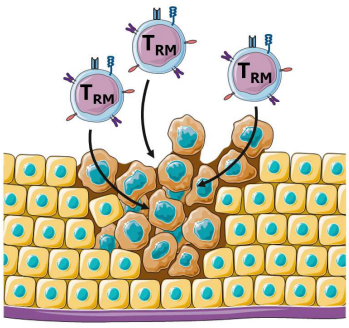
T_{RM} cell function



- High viral load symptom scores are associated with lower levels of antigen-specific T_{RM} cells
- The more antigen specific T_{RM} cells are present, the lower the viral load and symptom score

T_{RM} cell function

Tissue penetrating properties, durability, and cytotoxic capacity could make T_{RM} cells ideal in tumour therapy



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T_{RM} cell function

Tissue penetrating properties, durability, and cytotoxic capacity could make T_{RM} cells ideal in tumour therapy

nature immunology

Tissue-resident memory T cells at the center of immunity to solid tumors

Amsen D. *et al., Nat Immunol.* 2018; 19(6):538-546

nature cancer

Resident and circulating memory T cells persist for years in melanoma patients with durable responses to immunotherapy

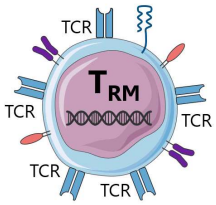
Han J. *et al., Nat Cancer.* 2021; 2(3):300-311

T_{RM} cell function

Science Immunology

Resident memory T cells in the skin mediate durable immunity to melanoma

Malik B. *et al., Sci Immunol.* 2017; 2(10):eaam6346



T_{RM} cells express many T cell receptors that may be triggered by immunotherapies

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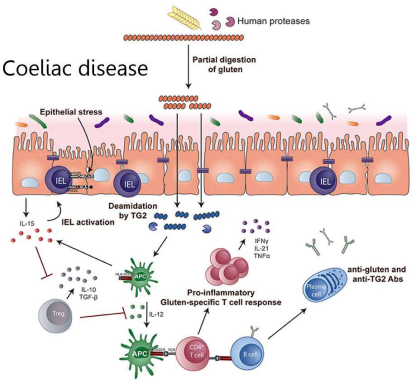
Aberrant T_{RM} cell roles

Tissue specific chronic immunity/autoimmunity

Coeliac disease



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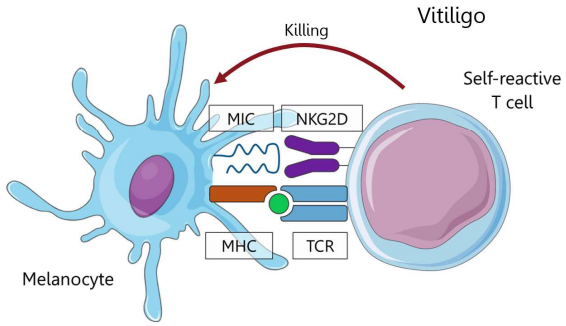
Aberrant T_{RM} cell roles

Tissue specific chronic immunity/autoimmunity



Aberrant T_{RM} cell roles

Article

Cell

Chronic Inflammation Permanently Reshapes Tissue-Resident Immunity in Celiac Disease

Mayassi T. *et al., Cell.* 2019; 176(5):967-981.e19

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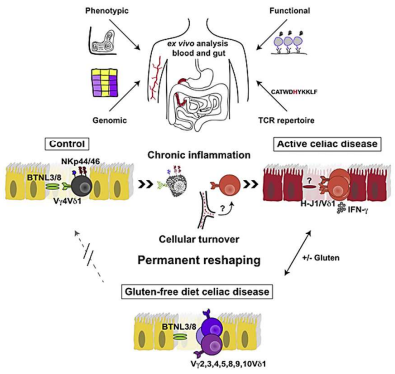
Aberrant T_{RM} cell roles

Tissue-resident lymphocyte turnover



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Aberrant T_{RM} cell roles

Gastroenterology

Interferon-Gamma–Producing $CD8^+$ Tissue Resident Memory T Cells Are a Targetable Hallmark of Immune Checkpoint Inhibitor–Colitis

Sasson S. *et al., Gastroent.* 2021; 161(4): 1229–1244.e9

Aberrant T_{RM} cell roles

TLCR

Vitiligo-like depigmentation after pembrolizumab treatment in patients with non-small cell lung cancer: a case report

Yun S. *et al., Transl Lung Cancer Res.* 2020; 9(4): 1585–1590

JCRP

Vitiligo after immune checkpoint inhibitor therapy in a woman with metastatic melanoma

Yang MH. And Chang DY. *Journ Canc Res Prac.* 2018; 5(4):161-164

nature cancer

Resident and circulating memory T cells persist for years in melanoma patients with durable responses to immunotherapy

Han J. *et al., Nat Cancer.* 2021; 2(3):300-311

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Aberrant T_{RM} cell roles

- "Of patients with melanoma who receive immunotherapy, long-term survivors are frequently found to develop melanoma-associated vitiligo, an autoimmune cutaneous side effect"
- Vitiligo associated with anti-melanoma activity T_{RM} cells 9 years after treatment in skin

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Concluding remarks

1. CD8 T_{RM} have similar transcriptional profiles in different organs: but there are differences
2. Markers such as CD103, CD49a are not absolute markers
3. The origin of T_{RM} cells is not yet understood
4. T_{RM} cells make an important contribution to control local pathogen load
5. T_{RM} cells have potential in tumour therapy
6. T_{RM} cells can have a pathogenic role in tissue-associated autoimmune disorders
7. T_{RM} cell activity maybe triggered by some checkpoint inhibitor therapies
8. There are also CD4 T_{RM} cells; these are less defined and may reflect Th subsets

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