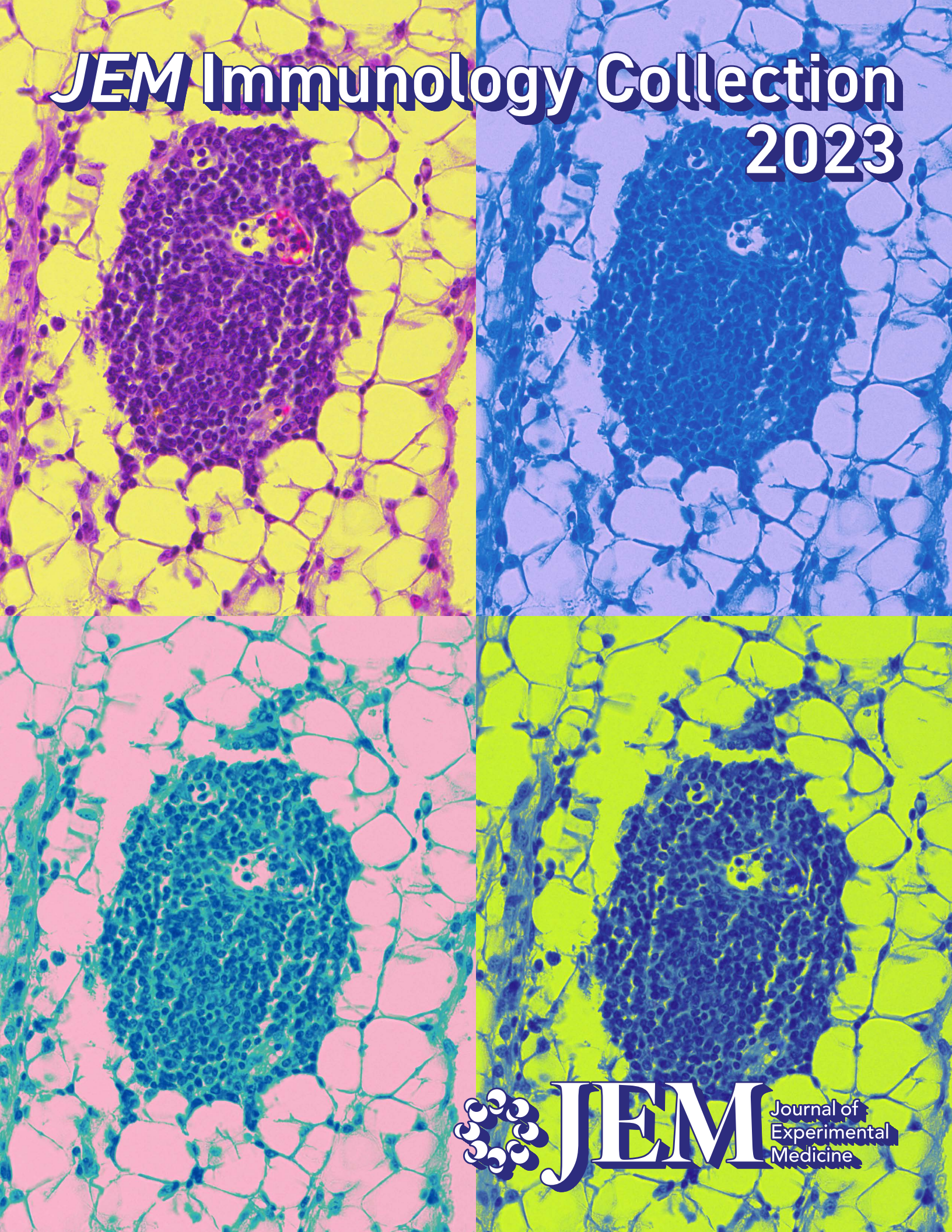
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"What's happening now is allowing us to have these conversations about the role of academia, and we are finally addressing why we need more funding for academia."

– Sara Suliman, UCSF

"Women have to be a bit selfish and strategic about our time, and not buckle to peer pressure and be expected to run the committees or do all of these sorts of things that society has traditionally expected women to do."

– Kate Schroder, University of Queensland

"I see my role as helping to really empower their questions, empower their curiosity, and empower their motivation. Those are the general mentorship characteristics I try to follow."

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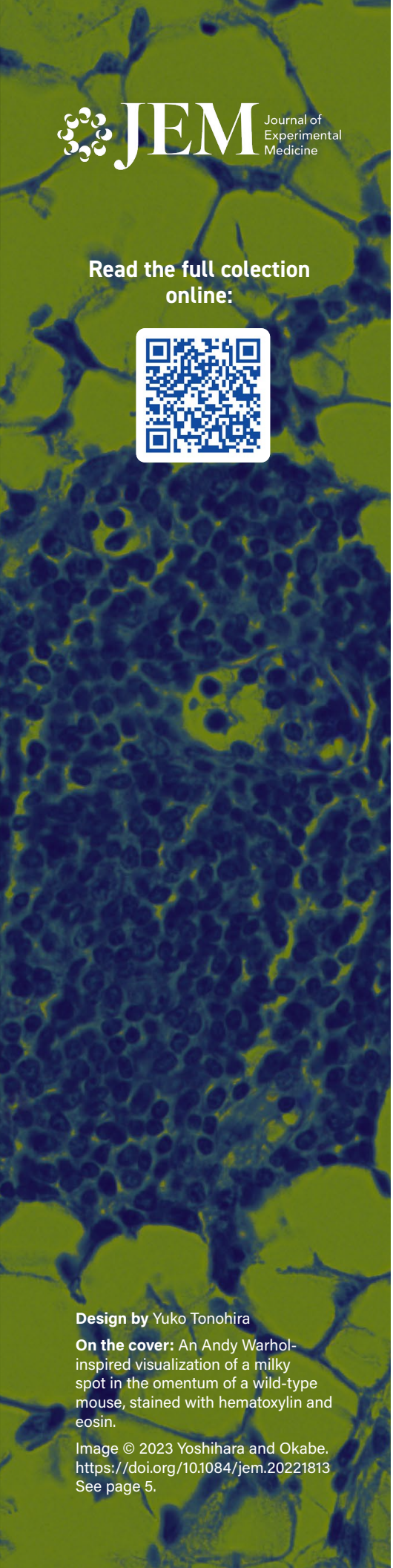

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Design by Yuko Tonohira

On the cover: An Andy Warhol-inspired visualization of a milky spot in the omentum of a wild-type mouse, stained with hematoxylin and eosin.

https://doi.org/10.1084/jem.20221813
See page 5.

JEM IMMUNOLOGY COLLECTION 2023

As part of *Journal of Experimental Medicine*'s continued efforts to foster seminal immunology studies over the years, the editorial team is pleased to present a special collection of recent immunology research articles. This special collection covers a broad range of topics including lymphocyte trafficking, activation and residency on mucosal sites, food allergy treatment and homeostatic networks responding to diet, genomic and transcriptional reorganization in infection and cancer, SARS-CoV-2 suppression of cytolytic activity, and natural killer cell adaptive-like phenotype. If you enjoy this collection, we encourage you to scan the QR codes to view the articles online and sign up for email alerts to receive the latest research. If you are interested in submitting work in this field to *JEM*, we encourage you to contact our editorial office via jem@rockefeller.edu or +1 212-327-8575.

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JEM Journal of Experimental Medicine

PROFILING THE INTESTINAL INTERACTOME'S RESPONSE TO A WESTERN DIET

The small intestine plays a key role in immunity and mediates inflammatory responses to high fat diets. We have used single-cell RNA-sequencing (scRNA-seq) and statistical modeling to examine gaps in our understanding of the dynamic properties of intestinal cells and underlying cellular mechanisms.

Our scRNA-seq and flow cytometry studies of different layers of intestinal cells revealed new cell subsets and modeled developmental trajectories of intestinal intraepithelial lymphocytes, lamina propria lymphocytes, conventional dendritic cells, and enterocytes.

As compared to chow-fed mice, a high-fat high-sucrose (HFHS) "Western" diet resulted in the accumulation of specific immune cell populations and marked changes to enterocytes nutrient absorption function.

Utilizing ligand–receptor analysis, we profiled high-resolution intestine interaction networks across all immune cell and epithelial structural cell types in mice fed chow or HFHS diets. These results revealed novel interactions and communication hubs among intestinal cells and their potential roles in local as well as systemic inflammation.

ORIGINAL PAPER

Wang, Y.-C., Y. Cao, C. Pan, Z. Zhou, L. Yang, and A.J. Lusis. 2023. Intestinal cell type-specific communication networks underlie homeostasis and response to Western diet. *J. Exp. Med.* 220 (5): e20221437. https://doi.org/10.1084/jem.20221437

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RETINOIC ACID–PRODUCING CELLS RECRUIT LYMPHOCYTES TO OMENTAL MILKY SPOTS

Lymphoid clusters in visceral adipose tissue omentum, known as milky spots, play a central role in immunological defense in the abdomen. Milky spots exhibit a hybrid nature between secondary lymph organs and ectopic lymphoid tissues, yet their development and maturation mechanisms are poorly understood.

We identified a subset of fibroblastic reticular cells (FRCs) that are uniquely present in omental milky spots. These FRCs were characterized by the expression of the retinoic acid–converting enzyme, *Aldh1a2*, and the endothelial cell marker, *Tie2*, in addition to canonical FRC-associated genes. Diphtheria toxin–mediated ablation of *Aldh1a2*$^+$ FRCs resulted in the alteration of milky spot structure with a significant reduction in size and cellularity.

Mechanistically, *Aldh1a2*$^+$ FRCs regulated the display of the chemokine CXCL12 on high endothelial venules, which recruit blood-borne lymphocytes from circulation. We further found that *Aldh1a2*$^+$ FRCs are required for the maintenance of peritoneal lymphocyte composition. These results illustrate the homeostatic roles of FRCs in the formation of non-classical lymphoid tissues.

ORIGINAL PAPER

Yoshihara, T., and Y. Okabe. 2023. *Aldh1a2*$^+$ fibroblastic reticular cells regulate lymphocyte recruitment in omental milky spots. *J. Exp. Med.* 220 (5): e20221813. https://doi.org/10.1084/jem.20221813

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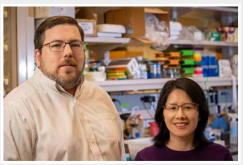
RETINOIC ACID LICENSES T CELLS TO BECOME GUT-RESIDENT MEMORY CELLS

CD8 tissue-resident memory T (T_{RM}) cells provide frontline protection at barrier tissues; however, mechanisms regulating T_{RM} cell development are not completely understood. Priming dictates the migration of effector T cells to the tissue, while factors in the tissue induce in situ T_{RM} cell differentiation. Whether priming also regulates in situ T_{RM} cell differentiation uncoupled from migration is unclear.

We demonstrate that T cell priming in the mesenteric lymph nodes (MLN) regulates CD103$^+$ T_{RM} cell differentiation in the intestine. In contrast, T cells primed in the spleen were impaired in the ability to differentiate into CD103$^+$ T_{RM} cells after entry into the intestine.

MLN priming initiated a CD103$^+$ T_{RM} cell gene signature and licensed rapid CD103$^+$ T_{RM} cell differentiation in response to factors in the intestine. Licensing was regulated by retinoic acid signaling and primarily driven by factors other than CCR9 expression and CCR9-mediated gut homing. Thus, the MLN is specialized to promote intestinal CD103$^+$ CD8 T_{RM} cell development by licensing in situ differentiation.

RESEARCHER DETAILS



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Qiu, Z., C. Khairallah, T.H. Chu, J.N. Imperato, X. Lei, G. Romanov, A. Atakilit, L. Puddington, and B.S. Sheridan. 2023. Retinoic acid signaling during priming licenses intestinal CD103$^+$ CD8 T_{RM} cell differentiation. *J. Exp. Med.* 220 (5): e20210923. https://doi.org/10.1084/jem.20210923

CTCF REORGANIZES THE GENOME TO PROMOTE CYTOTOXIC T CELL DIFFERENTIATION

Differentiation of effector CD8$^+$ T cells is instructed by stably and dynamically expressed transcription regulators. Here we show that naive-to-effector differentiation was accompanied by dynamic CTCF redistribution and extensive chromatin architectural changes.

Upon CD8$^+$ T cell activation, CTCF acquired de novo binding sites and anchored novel chromatin interactions, and these changes were associated with increased chromatin accessibility and elevated expression of cytotoxic program genes including *Tbx21*, *Ifng*, and *Klrg1*. CTCF was also evicted from its ex-binding sites in naive state, with concomitantly reduced chromatin interactions in effector cells, as observed at memory precursor–associated genes including *Il7r*, *Sell*, and *Tcf7*.

Genetic ablation of CTCF indeed diminished cytotoxic gene expression, but paradoxically elevated expression of memory precursor genes. Comparative Hi-C analysis revealed that key memory precursor genes were harbored within insulated neighborhoods demarcated by constitutive CTCF binding, and their induction was likely due to disrupted CTCF-dependent insulation. CTCF thus promotes cytotoxic effector differentiation by integrating local chromatin accessibility control and higher-order genomic reorganization.

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Liu, J., S. Zhu, W. Hu, X. Zhao, Q. Shan, W. Peng, and H.-H. Xue. 2023. CTCF mediates CD8$^+$ effector differentiation through dynamic redistribution and genomic reorganization. *J. Exp. Med.* 220 (4): e20221288. https://doi.org/10.1084/jem.20221288

JEM Journal of Experimental Medicine

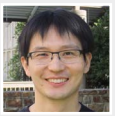
MYELOID-LIKE B CELLS BOOST EMERGENCY MYELOPOIESIS

Emergency myelopoiesis (EM) is a hematopoietic response against systemic infections that quickly supplies innate immune cells. As lymphopoiesis is strongly suppressed during EM, the role of lymphocytes in that process has not received much attention.

We found that myeloid-like B cells (M-B cells), which express myeloid markers, emerge in the bone marrow (BM) after the induction of EM. M-B cells were mainly derived from pre-B cells and preferentially expressed IL-10, which directly stimulate hematopoietic progenitors to enhance their survival and myeloid-biased differentiation.

Indeed, lacking IL-10 in B cells, blocking IL-10 in the BM with a neutralizing antibody, and deleting the IL-10 receptor in hematopoietic progenitors significantly suppressed EM, which failed to clear microbes in a cecal ligation and puncture model. Thus, a distinct B cell subset generated during infection plays a pivotal role in boosting EM, which suggests the on-demand reinforcement of EM by adaptive immune cells.

RESEARCHER DETAILS



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Kanayama, M., Y. Izumi, M. Akiyama, T. Hayashi, K. Atarashi, A. Roers, T. Sato, and T. Ohteki. 2023. Myeloid-like B cells boost emergency myelopoiesis through IL-10 production during infection. *J. Exp. Med.* 220 (4): e20221221. https://doi.org/10.1084/jem.20221221

WNK1 REGULATES B CELL ANTIBODY RESPONSES

Migration and adhesion play critical roles in B cells, regulating recirculation between lymphoid organs, migration within lymphoid tissue, and interaction with $CD4^+$ T cells. However, there is limited knowledge of how B cells integrate chemokine receptor and integrin signaling with B cell activation to generate efficient humoral responses.

We show that the WNK1 kinase, a regulator of migration and adhesion, is essential in B cells for T-dependent and -independent antibody responses. We demonstrate that WNK1 transduces signals from the BCR, CXCR5, and CD40, and using intravital imaging, we show that WNK1 regulates migration of naive and activated B cells, and their interactions with T cells.

Unexpectedly, we show that WNK1 is required for BCR- and CD40-induced proliferation, acting through the OXSR1 and STK39 kinases, and for efficient B cell–T cell collaboration in vivo. Thus, WNK1 is critical for humoral immune responses, by regulating B cell migration, adhesion, and T cell–dependent activation.

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Hayward, D.A., L. Vanes, S. Wissmann, S. Sivapatham, H. Hartweger, J.B. O'May, L.L. de Boer, R. Mitter, R. Köchl, J.V. Stein, and V.L.J. Tybulewicz. 2023. B cell–intrinsic requirement for WNK1 kinase in antibody responses in mice. *J. Exp. Med.* 220 (3): e20211827. https://doi.org/10.1084/jem.20211827

REGULATORY T CELLS SUPPRESS PROTEIN SYNTHESIS IN CD4 EFFECTOR CELLS

Regulatory T cells (Tregs) suppress the activation and subsequent effector functions of CD4 effector T cells (Teffs). However, molecular mechanisms that enforce Treg-mediated suppression in CD4 Teff are unclear.

We found that Tregs suppressed activation-induced global protein synthesis in CD4 Teffs prior to cell division. We analyzed genome-wide changes in the transcriptome and translatome of activated CD4 Teffs. We show that mRNAs encoding for the protein synthesis machinery are regulated at the level of translation in activated CD4 Teffs by Tregs. Tregs suppressed global protein synthesis of CD4 Teffs by specifically inhibiting mRNAs of the translation machinery at the level of mTORC1-mediated translation control through concerted action of immunosuppressive cytokines IL-10 and TGFβ.

Lastly, we found that the therapeutic targeting of protein synthesis with the RNA helicase eIF4A inhibitor rocaglamide A can alleviate inflammatory CD4 Teff activation caused by acute Treg depletion in vivo. These data show that peripheral tolerance is enforced by Tregs through mRNA translational control in CD4 Teffs.

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So, L., K. Obata-Ninomiya, A. Hu, V.S. Muir, A. Takamori, J. Song, J.H. Buckner, R. Savan, and S.F. Ziegler. 2023. Regulatory T cells suppress CD4⁺ effector T cell activation by controlling protein synthesis. *J. Exp. Med.* 220 (3): e20221676. https://doi.org/10.1084/jem.20221676

BCL6 MAINTAINS CCR6⁺ ILC3 LINEAGE IDENTITY

Innate lymphoid cells (ILC) are similar to T helper (Th) cells in expression of cytokines and transcription factors. For example, RORγt is the lineage-specific transcription factor for both ILC3 and Th17 cells. However, the ILC counterpart for BCL6-expressing T follicular helper (Tfh) cells has not been defined.

We report that in the ILC compartment, BCL6 is selectively co-expressed with not only CXCR5 but also RORγt and CCR6 in ILC3 from multiple tissues. BCL6-deficient ILC3 produces enhanced levels of IL-17A and IL-22. More importantly, phenotypic and single-cell ATAC-seq analysis show that absence of BCL6 in mature ILC3 increases the numbers of ILC1 and transitional cells co-expressing ILC3 and ILC1 marker genes. A lineage-tracing experiment further reveals BCL6⁺ ILC3 to ILC1 trans-differentiation under steady state.

Finally, microbiota promote BCL6 expression in colonic CCR6⁺ ILC3 and thus reinforce their stability. Collectively, our data have demonstrated that CCR6⁺ ILC3 have both Th17 and Tfh programs and that BCL6 expression in these cells functions to maintain their lineage identity.

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ORIGINAL PAPER
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JEM Journal of Experimental Medicine

SARS-CoV-2 SPIKE PROTEIN INHIBITS IMMUNE SYNAPSE ASSEMBLY

Cytotoxic T lymphocyte (CTL)-mediated killing of virally infected or malignant cells is orchestrated at the immune synapse (IS). We hypothesized that SARS-CoV-2 may target lytic IS assembly to escape elimination.

We show that human $CD8^+$ T cells upregulate the expression of ACE2, the Spike receptor, during differentiation to CTLs. CTL preincubation with the Wuhan or Omicron Spike variants inhibits IS assembly and function, as shown by defective synaptic accumulation of TCRs and tyrosine phosphoproteins as well as defective centrosome and lytic granule polarization to the IS, resulting in impaired target cell killing and cytokine production.

These defects were reversed by anti-Spike antibodies interfering with ACE2 binding and reproduced by ACE2 engagement by angiotensin II or anti-ACE2 antibodies, but not by the ACE2 product Ang (1-7). IS defects were also observed ex vivo in CTLs from COVID-19 patients.

These results highlight a new strategy of immune evasion by SARS-CoV-2 based on the Spike-dependent, ACE2-mediated targeting of the lytic IS to prevent elimination of infected cells.

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Onnis, A., E. Andreano, C. Cassioli, F. Finetti, C. Della Bella, O. Staufer, E. Pantano, V. Abbiento, G. Marotta, M.M. D'Elios, R. Rappuoli, and C.T. Baldari. 2023. SARS-CoV-2 Spike protein suppresses CTL-mediated killing by inhibiting immune synapse assembly. *J. Exp. Med.* 220 (2): e20220906. https://doi.org/10.1084/jem.20220906

REGULATION OF HUMAN ADAPTIVE-LIKE NK CELL DEVELOPMENT

Human adaptive-like natural killer (NK) cells express low levels of FcεRIγ ($FcR\gamma^{-/low}$) and are reported to accumulate during COVID-19 infection; however, the mechanism underlying and regulating FcRγ expression in NK cells has yet to be fully defined.

We observed lower FcRγ protein expression in NK cell subsets from lung transplant patients during rapamycin treatment, suggesting a link with reduced mTOR activity. Further, $FcR\gamma^{-/low}$ NK cell subsets from healthy donors displayed reduced mTOR activity. We discovered that FcRγ upregulation is dependent on cell proliferation progression mediated by IL-2, IL-15, or IL-12, is sensitive to mTOR suppression, and is inhibited by TGFβ or IFNα.

Accordingly, the accumulation of adaptive-like $FcR\gamma^{-/low}$ NK cells in COVID-19 patients corresponded to increased TGFβ and IFNα levels and disease severity. Our results show that an adaptive-like NK cell phenotype is induced by diminished cell proliferation and has an early prognostic value for increased TGFβ and IFNα levels in COVID-19 infection associated with disease severity.

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ORIGINAL PAPER

Shemesh, A., Y. Su, D.R. Calabrese, D. Chen, J. Arakawa-Hoyt, K.T. Roybal, J.R. Heath, J.R. Greenland, and L.L. Lanier. 2022. Diminished cell proliferation promotes natural killer cell adaptive-like phenotype by limiting FcεRIγ expression. *J. Exp. Med.* 219 (11): e20220551. https://doi.org/10.1084/jem.20220551

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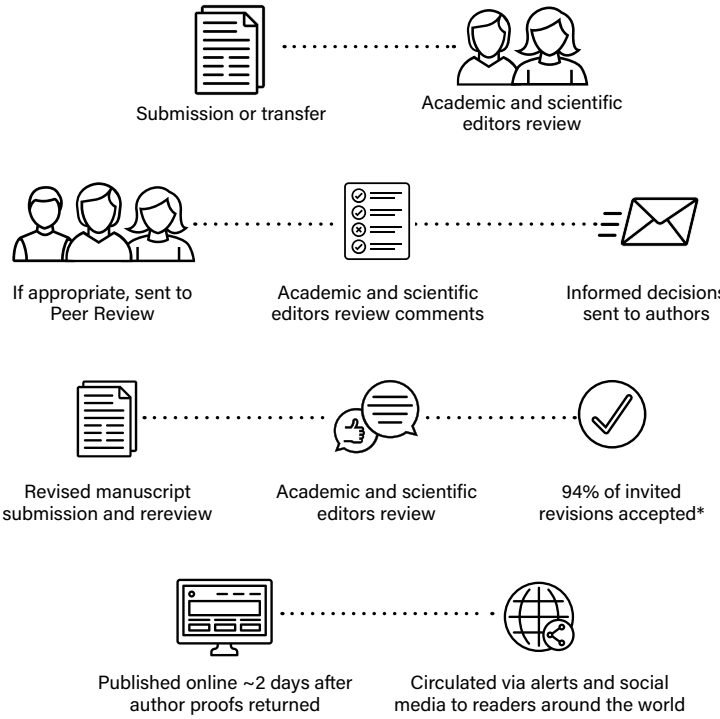

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