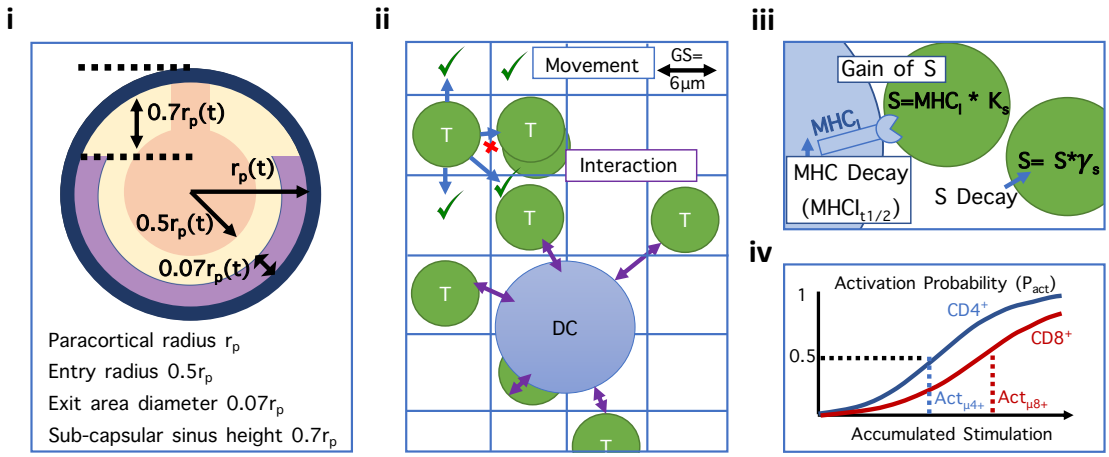
Modelling the effects of lymph node swelling on T-cell response.

# Supplementary File 1 : Supplementary Methods A

**Fig A Modelling Methods.** (i). Definitions of different areas of the paracortex are based on the overall paracortical radius, and therefore alter in volume during expansion. (ii) Lattice based DC and TC interaction. (iii). During interactions, TCs gain stimulation at a rate proportional to the presented antigenic signal, which is itself decaying. Accumulated TC simulation also undergoes constant decay. (iv). Accumulated stimulation is to determine probability of TC activation or differentiation, dependent on the satisfaction of other criteria.




## 1.1 TC recruitment

Under non-inflammatory conditions, it was assumed that TC entry and exit remain constant and TCs occupy a constant percentage (55%) of the total paracortical volume. The model represents a LN of 0.113-0.268 $mm^3$, implying a LN mass of 0.18-0.44mg (based on collaborative unpublished measurements of murine popliteal LN mass versus volume). Reported lymphocyte recruitment for a popliteal LN of 1.15g is $4x10^7$ lymphocytes/hour and up to 40% of lymphocytes are B cells [1–3]. The model represents half a paracortex, therefore TC recruitment rate was estimated as 1950-9000 TCs/hour under non-antigenic conditions. Naive TC transit time through the LN ($T_{res}$) was estimated as 6-24 hours [4].

## 1.2 Agents and agent migration

The agents were designated as members of the TC or DC class (Fig A). Simulated DCs appear in the paracortex at a constant entry rate for 2 days, subsiding over the following 12 hours. Entry rate of DCs was scaled from counts of migrating DCs and initial TCs in a murine LN post-immunisation,

with DCs totalling 4% of cells present [5]. TC migration was assumed to follow a random walk with pauses. Previous models have described TC migration with Brownian motion, a random-walk with persistence,run and tumble, and Lévy walks amongst other methods, partly due to differing reports of *in-vivo* migration. [6–9].

## 1.3 Agent interaction and signal integration

During TC-DC interaction, TCs remain stationary. Antigenic signal is presented by the DCs in the form of representative values of MHCI or MHCII, and decays with time (t) with the form :

$$MHCI(t) = MHCI_i(0.5)^{\frac{t}{MHCI_{\frac{1}{2}}}} \tag{1}$$

$MHCII_i$ is the initial MHCI or initial MHCII presented with estimated MHC half-lives $MHCI_{1/2}$ and $MHCII_{1/2}$ respectively. During cognate TC-DC interaction, $CD4^+/CD8^+$ TCs gain (S) at a rate proportional to the MHCI or MHCII signal respectively (Fig A.iii). Accumulated stimulation decays at a constant rate. Total change in TC stimulation is therefore given according to the first order rate equation:

$$\frac{dS}{dt} = K_s\, MHCII(t) - \lambda_S\, S(t) \tag{2}$$

Where $K_s$ is a rate constant and $\lambda_S$ is a decay factor. Accumulated simulation decays to a minimal value of S=1 to allow differentiation between cognate TCs that gain and lose simulation (S=1) and those that never gain simulation (S=0). Probability of cognate $CD_{4^+}$ activation ($P_{a4^+}$) or cognate $CD_{8^+}$ activation ($P_{a8^+}$) is calculated with a sigmoidal function given by:

$$P_{a4^+} = \frac{1}{1 + e^{\frac{-S - Act\mu_4}{Actl_4}}} \tag{3}$$

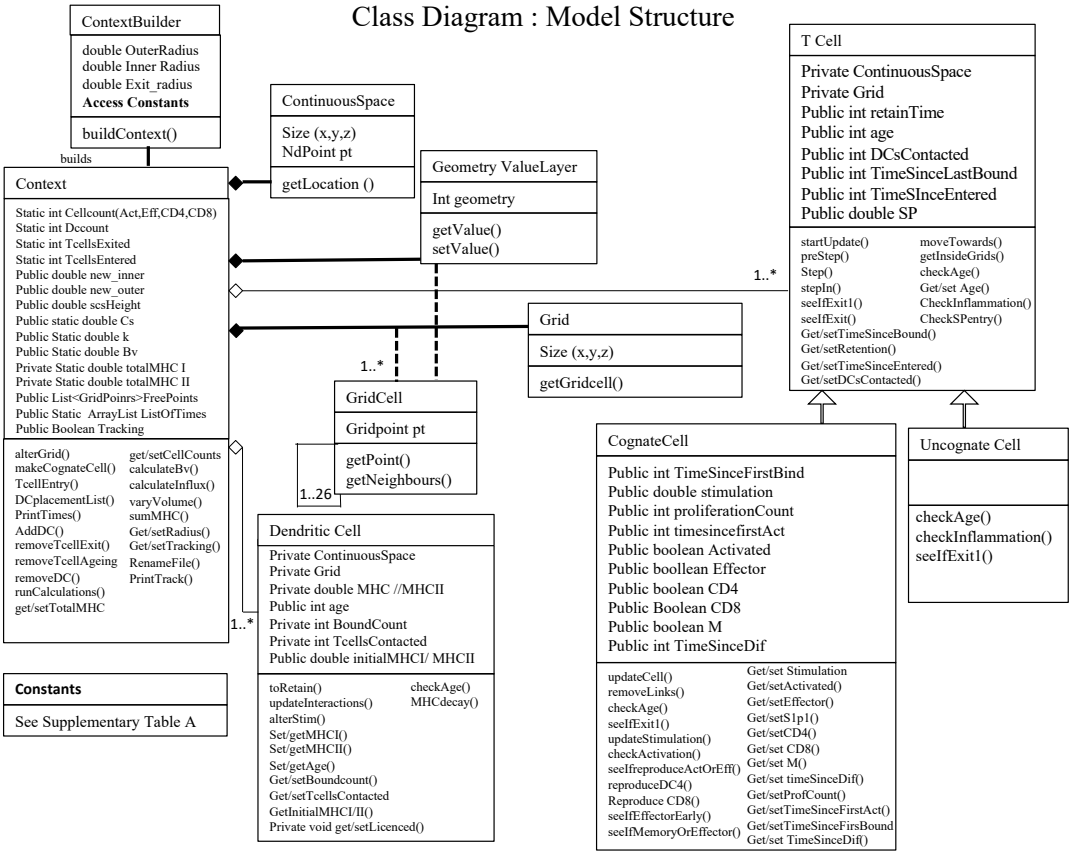
Parameter Act$\mu_4$ determines the value of S required for 50% probability of activation and Act$l_4$ determines steepness of sigmoid inflection (Fig A.iv). Activation probability for $CD8^+$ TCs ($P_{a8^+}$) is determined with a sigmoid curve using a lower inflection point, (Act$\mu_8$), than for $CD4^+$ TCs, unless the interacting agDC is licenced (see 1.4). Model parameters were estimated such that TC activation became apparent 8-15 hours post DC-arrival [10–12]. This method of signal integration and the subsequent progressive patterns of TC proliferation and differentiation is supported by *in-vivo* observations and modelling descriptions [12–15]. It is assumed that co-stimulatory requirements are met as agDCs are highly efficient antigen-presenting cells.

Post-activation, proliferation is possible every 11 ($CD4^+$) or 9 ($CD8^+$) $\pm$1hr [16–19]. Differentiation into effector or memory cells is possible after $>=4$ divisions, with differentiation probability determined with a second set of sigmoidal probability curves with midpoint Dif$\mu_{4+}$ and Dif$\mu_{8+}$ respectively [20,21]. Greater $CD4^+$ TCs dependence on continued stimulation for differentiation than $CD8^+$ TCs was implemented by using a higher minimum threshold of accumulated stimulation for $CD4^+$ differentiation than for $CD8^+$ TCs [22–26]. Effectors TCs that underwent $< 8$ proliferations were less likely to differentiate into memory cells than those that underwent $>8$ proliferations. This was implemented by assigning differentiation ratios of $dif_{early}$ and $dif_{late}$ to the two different subsets ($<=8$ or $>8$ divisions).

During TC activation and proliferation, $S1P_1r$ expression was estimated from several *in-silico* studies. Expression change was considered following TC migration velocity into areas of high S1P

concentration, changes in TC egress from the LN and changes in $S1P_1R$ expression relative to naive $S1P_1r$ expression following TC activation and with subsequent proliferation (Fig 2C.iii) [27–29].

**Fig B A class diagram displaying the underlying ABM structure.** The model is constructed using instructions in the 'context builder' class. The entire modelling domain is described by the context class, and each compartment of the domain is described by the GridCell class. In a 3D simulation, each grid cell can be queried to identify the 26 neighbouring grids and how many agents they contain. The TC class is a template for the TC object produced and is instantiated thousands of times to create TCs with the same variables but slightly different values. A subclass of cognate TCs extends the template with more methods and variables relating to interaction and proliferative response.



# S1 File Supplementary Tables

## Table A Parameters that were not varied in the global sensitivity analysis

| Symbol | Parameter | Value | Reference |
|---|---|---|---|
| | Model Geometry | | |
| $r_p$ | Initial paracortex radius | 200$\mu$m | [30,31] |
| - | Entry radius | 0.5 $r_p$ | [30,31] |
| - | Exit radius | 0.07$r_p$ | [30,31] |
| - | Sub Capsular Sinus height | 0.7$r_p$ | [30,31] |
| GS | Grid Size | 6$\mu$m | - |
| | TC Properties | | |
| - | Initial occupation | 55% | [32] |
| - | Radius | 3.3$\mu$m | [33] |
| - | Ratio CD4:CD8 | 0.7:0.3 | [30,31] |
| - | Lifespan naive | 0.5 $r_p$ | [34] |
| - | Lifespan naive | 0.5 $r_p$ | [35] |
| - | TC entry Afferent:HEV ratio | 0.1:0.9 | [36,37] |
| Act$l_{4+}$ | Slope of CD4$^+$ activation curve | -69.81 | - |
| Act$l_{8+}$ | Slope of CD4$^+$ activation curve | -80.71 | - |
| Dif$l_{4+}$ | Slope of CD4$^+$ differentiation curve | -17.26 | - |
| Dif$l_{8+}$ | Slope of CD8$^+$ differentiation curve | -13.58 | - |
| | T cell movement | | |
| $\beta$ | Probability of movement | 0.6 | [20,38–41] |
| $P_e$ | Probability of egress | 0.0126 | - |
| $\gamma$ | Max cells per grid | 2 | - |
| $T_{res}$ | TC residence time | 24hrs | [4,42] |
| | DC properties | | |
| - | DC span | 2 grids | [33,43,44] |
| - | DC Lifespan | 2.5days | [5,45,46] |

**Table B Parameters varied in the global sensitivity analysis. Continued overleaf.**

| Symbol | Parameter Description | Default | Min | Max | Mean | SD | Distrib. | Ref |
|---|---|---|---|---|---|---|---|---|
| | TC response parameters | | | | | | | |
| $\text{Act}\mu_4$ | $CD4^+$ activation curve mean | 120 | 70 | 230 | - | - | Unif | [47–52] |
| $\text{Act}\mu_8$ | $CD8^+$ activation curve mean | 140 | 90 | 250 | - | - | Unif | [47–52] |
| $\text{Dif}\mu_4$ | $CD4^+$ differentiation curve mean | 60 | 30 | 90 | - | - | Unif | [47–52] |
| $\text{Dif}\mu_8$ | $CD8^+$ differentiation curve mean | 40 | 20 | 60 | - | - | Unif | [47–52] |
| $\text{TP}_4$ | Min time between $CD4^+$ proliferations (hrs) | 11 | - | - | 11 | 1.16 | Norm | [16–19] |
| $\text{TP}_8$ | Min time between $CD8^+$ proliferations (hrs) | 7 | - | - | 7 | 0.88 | Norm | [16,17] |
| $\text{Max}_{P8}$ | Max proliferations $CD8^+$ | 16 | - | - | 16 | 1.2 | Norm | [25,53–55] |
| $\text{Max}_{P4}$ | Max proliferations $CD4^+$ | 10 | - | - | 10 | 1.2 | Norm | [17–19] |
| $\text{Dif}_{early}$ | Early Memory:Effector cell differentiation | 0.01 | 0.001 | 0.02 | 0.01 | - | Exp | [56] |
| $\text{Dif}_{late}$ | Late Memory:Effector cell differentiation | 0.04 | 0.01 | 0.08 | - | - | Unif | [56] |
| | TC interaction dynamics | | | | | | | |
| $\text{T}_{NC}$ | Mean non-cognate T-DC interaction (min) | 3.5 | - | - | 3.5 | 1 | Norm | [46,57] |
| $\text{T}_{short}$ | Short cognate TC-DC interaction (min) | 10-15 | - | - | 10 | 3 | Norm | [11,46,57] |
| $\text{T}_{long}$ | Long cognate TC-DC interaction (min) | 50-70 | - | - | 50 | 12 | Norm | [10–12,58] |
| $\text{T}_{change}$ | Time TCs switch to long interactions (hr) | 8 | - | - | 8 | 1 | Norm | [10–12,58] |
| $\text{B}_{max}$ | Max TCs a DC can bind per-step | 3 | 1 | 5 | - | - | Unif | - |
| $\text{B}_{step}$ | Max TCs a DC can bind | 15 | 4 | 20 | - | - | Unif | [59] |
| | TC Stimulation | | | | | | | |
| $\text{K}_s$ | Stim. gain coefficient | 0.015 | 0.005 | 0.02 | - | - | Unif | - |
| $\lambda$ | TC stim. decay factor | 0.99 | 0.99545 | 0.9999 | - | - | Unif | - |
| $\text{MHC}_i$ | Initial MHCI/II | 250 | 150 | 350 | - | - | Unif | [60–63] |
| $\text{MHCI}_{1/2}$ | MHCI half life (hrs) | 19.7 | - | - | 19.7 | 6 | Norm | [60,61] |
| $\text{MHCII}_{1/2}$ | MHCII half life (hrs) | 60 | - | - | 60 | 6 | Norm | [62,63] |
| $\text{F}_{cog}$ | Frequency of cognate TCs that enter | 1e-4 | 5e-5 | 1.5e-4 | - | - | Unif | [18,64–66] |
| $\Phi_{DC}$ | Total DCs entering as % of initial TCs | 0.04 | 0.02 | 0.06 | - | - | Unif | [5] |
| $\text{T}_{DCin}$ | DC entry duration (days) | 2.5 | 0.5 | 4.5 | - | - | Unif | [5] |

| Symbol | Parameter Description | Default | Min | Max | Mean | SD | Distrib. | Ref |
|---|---|---|---|---|---|---|---|---|
| | Sphingosine-1-phosphate receptor regulation | | | | | | | |
| $SP_{entry}$ | $S1P_1r$ expression post entry | 0.1 | 0.01 | 1 | - | - | Unif | [27,28,67] |
| $SP_{act}$ | $S1P_1r$ expression when activated | 0.01 | 0.001 | 0.02 | - | - | Unif | [27–29,67] |
| $S1_{early}$ | Effector $S1P_1r$ (Proliferation<=6) | 0.4 | 0.01 | 1 | - | - | Unif | [27,29] |
| $SP_{late}$ | Effector $S1P_1r$ (Proliferation>6) | 0.8 | 0.3 | 1.3 | - | - | Unif | [27,29] |
| $SP_{mem}$ | Memory $S1P_1rr$ | 1 | - | - | 1 | 0.1 | Norm | [27,29] |
| $SP_{IF}$ | $S1P_1r$ on all TCs during inflam. | 0.4 | 0.2 | 0.8 | - | - | Unif | - |
| $T_{Entry}$ | Time $S1P_1rr$ is low post-entry (min) | 60 | 13 | 120 | - | - | Unif | - |
| $T_{Inflam}$ | Time to alter $S1P_1r$ during inflam.(hr) | 4 | 1 | 7.5 | - | - | Unif | - |
| | T cell recruitment | | | | | | | |
| RT1 | recruitment increase stim. threshold | 2e4 | 2e4 | 1e5 | - | - | Unif | [68–71] |
| RT2 | Stim. threshold for max. recruitment | 4e5 | 2e5 | 2e6 | - | - | Unif | [68–71] |
| $R_F$ | Recruitment Factor | 3e-6 | 1e-6 | 4e-6 | - | - | Unif | [68–71] |
| | Paracortex expansion | | | | | | | |
| $V_{Max}$ | Max fold-volume increase | 1.00 | 2.00 | 2.50 | - | - | Unif | - |
| l | Rate of volume change around m | 7e-05 | 3e-05 | 1e-04 | - | - | Unif | - |
| $T_{mid}$ | No. of TCs for 50% max-volume | 120000 | 90000 | 150000 | - | - | Unif | - |

# References


[1] Cahill R, Frost H, Trnka Z. The effects of antigen on the migration of recirculating lymphocytes through single lymph nodes. J Exp Med. 1976;143(4):870–888.

[2] Habenicht LM, Albershardt TC, Iritani BM, Ruddell A. Distinct mechanisms of B and T lymphocyte accumulation generate tumor-draining lymph node hypertrophy. Oncoimmunology. 2016 08;5(8):e1204505.

[3] Battaglia A, Ferrandina G, Buzzonetti A, Malinconico P, Legge F, Salutari V, et al. Lymphocyte populations in human lymph nodes. Alterations in CD4(+) CD25(+) T regulatory cell phenotype and T-cell receptor Beta-repertoire. Immunology. 2003 11;110(3):304–312.

[4] Tomura M, Yoshida N, Tanaka J. Monitoring cellular movement in vivo with photoconvertible fluorescence protein 'Kaede' transgenic mice. PNAS. 2008;105(31):10871–6.

[5] Acton SE, Farrugia AJ, Astarita JL, Mourao-Sa D, Jenkins RP, Nye E, et al. Dendritic cells control fibroblastic reticular network tension and lymph node expansion. Nature. 2014 10;514(7523):498–502.

[6] Celli S, Day M, Müller AJ, Molina-Paris C, Lythe G, Bousso P. How many dendritic cells are required to initiate a T-cell response? Blood. 2012;120(19):3945–3948.

[7] Bogle G, Dunbar PR. Simulating T-cell motility in the lymph node paracortex with a packed lattice geometry. Imm Cell Biol. 2008 08;86(8):676–687.

[8] Brown LV, Gaffney EA, Wagg J, Coles MC. An in silico model of cytotoxic T-lymphocyte activation in the lymph node following short peptide vaccination. Journal of the Royal Society, Interface. 2018 03;15(140):2018.0041.

[9] Harris TH, Banigan EJ, Christian DA, Konradt C, Tait Wojno ED, Norose K, et al. Generalized Lévy walks and the role of chemokines in migration of effector CD8+ T cells. Nature. 2012 05;486:545–548.

[10] Hugues S, Fetler L, Bonifaz L, Helft J, Amblard F, Amigorena S. Distinct T cell dynamics in lymph nodes during the induction of tolerance and immunity. Nature Immunology. 2004 10;5:1235–42.

[11] Mempel TR, Henrickson SE, Von Andrian UH. T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. Nature. 2004;427(6970):154–9.

[12] Stoll S, Delon J, Brotz T, Germain R. Dynamic imaging of T cell-dendritic cell interactions in lymph nodes. Science. 2002;296(5574):1873–6.

[13] Germain RN, Stefanová I. THE DYNAMICS OF T CELL RECEPTOR SIGNALING: Complex Orchestration and the Key Roles of Tempo and Cooperation. Annual Review of Immunology. 1999 07;17(1):467–522.

[14] Rachmilewitz J, Lanzavecchia A. A temporal and spatial summation model for T-cell activation: signal integration and antigen decoding. Trends in Immunology. 2002;23(12):592–595.

[15] Lanzavecchia A, Sallusto F. Progressive differentiation and selection of the fittest in the immune response. Nature Reviews Immunology. 2002 12;2:982–7.

[16] De Boer RJ, Homann D, Perelson AS. Different Dynamics of CD4+ and CD8+ T Cell Responses During and After Acute Lymphocytic Choriomeningitis Virus Infection. The Journal of Immunology. 2003;171(8):3928–3935.

[17] Foulds KE, Zenewicz LA, Shedlock DJ, Jiang J, Troy AE, Shen H. Cutting Edge: CD4 and CD8 T Cells Are Intrinsically Different in Their Proliferative Responses. The Journal of Immunology. 2002;168(4):1528–1532.

[18] Nelson RW, Beisang D, Tubo NJ, Dileepan T, Wiesner DL, Nielsen K, et al. T cell receptor cross-reactivity between similar foreign and self peptides influences naïve cell population size and autoimmunity. Immunity. 2015 01;42(1):95–107.

[19] Tubo NJ, Pagán AJ, Taylor JJ, Nelson RW, Linehan JL, Ertelt JM, et al. Single Naive $CD4^+$ T Cells from a Diverse Repertoire Produce Different Effector Cell Types during Infection. Cell. 2013 04;153(4):785–796.

[20] Miller MJ, Wei SH, Parker I, Cahalan MD. Two-photon imaging of lymphocyte motility and antigen response in intact lymph node. Science. 2002;296(5574):1869–73.

[21] Linderman JJ, Riggs T, Pande M, Miller M, Marino S, Kirschner DE. Characterizing the Dynamics of CD4+ T Cell Priming within a Lymph Node. The Journal of Immunology. 2010;184(6):2873–2885.

[22] Schrum AG, Palmer E, Turka LA. Distinct temporal programming of naive CD4(+) T cells for cell division versus TCR-dependent death susceptibility by antigen-presenting macrophages. European journal of immunology. 2005 02;35(2):449–459.

[23] Wong P, Pamer EG. Cutting Edge: Antigen-Independent CD8 T Cell Proliferation. The Journal of Immunology. 2001;166(10):5864–5868.

[24] Kaech SM, Ahmed R. Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naïve cells. Nature Immunology. 2001 05;2:415–22.

[25] van Stipdonk MJB, Lemmens EE, Schoenberger SP. Naïve CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. Nature Immunology. 2001 05;2:423–9.

[26] Shaulov A, Murali-Krishna K. CD8 T Cell Expansion and Memory Differentiation Are Facilitated by Simultaneous and Sustained Exposure to Antigenic and Inflammatory Milieu. The Journal of Immunology. 2008;180(2):1131–1138.

[27] Pham T, Okada T, Matloubian M, Lo C, Cyster J. S1P 1 receptor signaling overrides retention mediated by Gi-coupled receptors to promote T cell egress. Immunity. 2008;28(1):122–133.

[28] Matloubian M, Lo C, Cinamon G, Lesneski M, Xu Y. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature. 2004;427(6972):355–60.

[29] Garris CS, Blaho VA, Hla T, Han MH. Sphingosine-1-phosphate receptor 1 signalling in T cells: trafficking and beyond. Immunology. 2014 07;142(3):347–353.

[30] Mueller SN, Germain RN. Stromal cell contributions to the homeostasis and functionality of the immune system. Nature Reviews Immunology. 2009 07;9:618–29.

[31] Kuka M, Iannacone M. The role of lymph node sinus macrophages in host defense. Annals of the New York Academy of Sciences. 2014;1319(1):38–46.

[32] He Y. Scanning electron microscope studies of the rat mesenteric lymph node with special reference to high-endothelial venules and hitherto unknown lymphatic labyrinth. Archivum histologicum Japonicum. 1985;(48):1–15.

[33] Tasnim H, Fricke GM, Byrum JR, Sotiris JO, Cannon JL, Moses ME. Quantitative Measurement of Naïve T Cell Association With Dendritic Cells, FRCs, and Blood Vessels in Lymph Nodes. Frontiers in Immunology. 2018;9:1571.

[34] Tough DF, Sprent J. Life span of naive and memory t cells. STEM CELLS. 1995;13(3):242–249.

[35] Sprent J, Tough DF. T Cell Death and Memory. Science. 2001;293(5528):245–248.

[36] Smith JB, McIntosh GH, Morris B. The traffic of cells through tissues: a study of peripheral lymph in sheep. Journal of Anatomy. 1970 07;107(Pt 1):87–100.

[37] Hall J, Morris B. The immediate effect of antigens on the cell output of a lymph node. British journal of experimental pathology. 1965;46(4):450–454.

[38] Park E, Peixoto A, Imai Y, Goodarzi A, Cheng G. Distinct roles for LFA-1 affinity regulation during T-cell adhesion, diapedesis, and interstitial migration in lymph nodes. Blood. 2010;115(8):1572–81.

[39] Boscacci R, Pfeiffer F, Gollmer K, Sevilla A. Comprehensive analysis of lymph node stroma-expressed Ig superfamily members reveals redundant and nonredundant roles for ICAM-1, ICAM-2, and VCAM-1 in lymphocyte homing. Blood. 2010;116(6):915–25.

[40] Park C, Hwang I, Sinha R, Kamenyeva O. Lymph node B lymphocyte trafficking is constrained by anatomy and highly dependent upon chemo-attractant desensitization. Blood. 2012;119(4):978–989.

[41] Girard JP, Moussion C, Förster R. HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes. Nat Rev Immunol. 2012;12(11):762–73.

[42] Catron DM, Itano AA, Pape KA, Mueller DL, Jenkins MK. Visualizing the first 50 hr of the primary immune response to a soluble antigen. Immunity. 2004;21(3):341–347.

[43] Nitschké M, Aebischer D, Abadier M, Haener S, Lucic M, Vigl B, et al. Differential requirement for ROCK in dendritic cell migration within lymphatic capillaries in steady-state and inflammation. Blood. 2012;120(11):2249–2258.

[44] Paharkova-Vatchkova V, Maldonado R, Kovats S. Estrogen Preferentially Promotes the Differentiation of CD11c+ CD11bintermediate Dendritic Cells from Bone Marrow Precursors. The Journal of Immunology. 2004;172(3):1426–1436.

[45] Kamath AT, Henri S, Battye F, Tough DF, Shortman K. Developmental kinetics and lifespan of dendritic cells in mouse lymphoid organs. Blood. 2002;100(5):1734–1741.

[46] Bousso P. T-cell activation by dendritic cells in the lymph node: lessons from the movies. Nature Reviews Immunology. 2008 09;8:675–84.

[47] Bajénoff M, Granjeaud S, Guerder S. The strategy of T cell antigen-presenting cell encounter in antigen-draining lymph nodes revealed by imaging of initial T cell activation. Journal of Experimental Med. 2003;198(5):715–724.

[48] Yoon H, Legge KL, Sung SsJ, Braciale TJ. Sequential Activation of CD8+ T Cells in the Draining Lymph Nodes in Response to Pulmonary Virus Infection. The Journal of Immunology. 2007;179(1):391–399.

[49] Lawrence CW, Braciale TJ. Activation, Differentiation, and Migration of Naive Virus-Specific CD8+ T Cells during Pulmonary Influenza Virus Infection. The Journal of Immunology. 2004;173(2):1209–1218.

[50] Demotz S, Grey H, Sette A. The minimal number of class II MHC-antigen complexes needed for T cell activation. Science. 1990;249(4972):1028–1030.

[51] Lee WT, Pasos G, Cecchini L, Mittler JN. Continued Antigen Stimulation Is Not Required During CD4+ T Cell Clonal Expansion. The Journal of Immunology. 2002;168(4):1682–1689.

[52] Arens R, Schoenberger SP. Plasticity in programming of effector and memory CD8(+) T-cell formation. Immunological reviews. 2010 05;235(1):190–205.

[53] Butz EA, Bevan MJ. Massive Expansion of Antigen-Specific CD8(+) T Cells during an Acute Virus Infection. Immunity. 1998 02;8(2):167–175.

[54] Murali-Krishna K, Altman JD, Suresh M, Sourdive DJD, Zajac AJ, Miller JD, et al. Counting Antigen-Specific CD8 T Cells: A Reevaluation of Bystander Activation during Viral Infection. Immunity. 1998 07;8(2):177–187.

[55] Busch DH, Pilip IM, Vijh S, Pamer EG. Coordinate Regulation of Complex T Cell Populations Responding to Bacterial Infection. Immunity. 1998 07;8(3):353–362.

[56] Williams MA, Bevan MJ. Shortening the Infectious Period Does Not Alter Expansion of CD8 T Cells but Diminishes Their Capacity to Differentiate into Memory Cells. The Journal of Immunology. 2004;173(11):6694–6702.

[57] Miller MJ, Hejazi AS, Wei SH, Cahalan MD, Parker I. T cell repertoire scanning is promoted by dynamic dendritic cell behavior and random T cell motility in the lymph node. Proc Natl Acad Sci USA. 2004;101(4):998–1003.

[58] von Andrian U, Mackay C. T-cell function and migration, two sides of the same coin. New England Journal of Medicine. 2000;343(14):1020–34.

[59] Bousso P, Robey E. Dynamics of CD8+ T cell priming by dendritic cells in intact lymph nodes. Nature immunology. 2003;4:579–585.

[60] Cella M, Salio M, Sakakibara Y, Langen H, Julkunen I, Lanzavecchia A. Maturation, Activation, and Protection of Dendritic Cells Induced by Double-stranded RNA. The Journal of Experimental Medicine. 1999 03;189(5):821–829.

[61] Kukutsch NA, Rossner S, Austyn JM, Schuler G, Lutz MB. Formation and Kinetics of MHC Class I-Ovalbumin Peptide Complexes on Immature and Mature Murine Dendritic Cells. Journal of Investigative Dermatology. 2000;115(3):449 – 453.

[62] Cella M, Engering A, Pinet V, Pieters J, Lanzavecchia A. Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature. 1997 08;388:782–7.

[63] Baumgartner C, Ferrante A, Nagaoka M, Gorski J, Malherbe LP. Peptide-MHC Class II Complex Stability Governs CD4 T Cell Clonal Selection. Journal of immunology (Baltimore, Md : 1950). 2010 01;184(2):573–581.

[64] Laouini D, Casrouge A, Dalle S, Lemonnier F, Kourilsky P, Kanellopoulos J. VI2 T Cell Repertoire of CD8+ Splenocytes Selected on Nonpolymorphic MHC Class I Molecules. The Journal of Immunology. 2000;165(11):6381–6386.

[65] Blattman JN, Antia R, Sourdive DJ, Wang X, Kaech SM, Murali-Krishna K, et al. Estimating the Precursor Frequency of Naive Antigen-specific CD8 T Cells. The Journal of Experimental Medicine. 2002 03;195(5):657–664.

[66] Jenkins MK, Moon JJ. The role of naïve T cell precursor frequency and recruitment in dictating immune response magnitude. Journal of Immunology (Baltimore, Md : 1950). 2012 05;188(9):4135–4140.

[67] Lo C, Xu Y, Proia R, Cyster J. Cyclical modulation of sphingosine-1-phosphate receptor 1 surface expression during lymphocyte recirculation and relationship to lymphoid organ transit. Journal of Experimental Medicine. 2005;2(201):291–301.

[68] Hay JB, Hobbs BB. The flow of blood to lymph nodes and its relation to lymphocyte traffic and the immune response. Journal of Experimental Medicine. 1977;145(1):31–44.

[69] Drayson MT, Smith ME. The sequence of changes in blood flow and lymphocyte influx to stimulated rat lymph nodes. Immunology. 1981;44:125–133.

[70] Mackay C, Marston W, Dudler L. Altered patterns of T cell migration through lymph nodes and skin following antigen challenge. European journal of Imm. 1992;22(9):2205–10.

[71] Webster B, Ekland EH, Agle LM, Chyou S, Ruggieri R, Lu TT. Regulation of lymph node vascular growth by dendritic cells. J Exp Med. 2006;203(8):1903–13.