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

Supplementary File 1.

Supplementary Methods.

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 The model represents a LN of 0.113-0.268 mm^3, implying a LN mass of 0.18-0.44mg (based on collaborative unpublished measurements of murine popliteal LN mass versus volume).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 (S Fig 1). 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 :

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

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

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

Where K_s is a rate constant and λ_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:

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

Parameter Actμ_4 determines the value of S required for 50% probability of activation and Actl_4 determines steepness of sigmoid inflection (Fig 2.D). Activation probability for CD8$^+$ TCs (P_{a8^+}) is determined with a sigmoid curve using a lower inflection point, (Actμ_8), than for CD4$^+$ TCs, unless the interacting agDC is licenced (see 2.4). 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 $>=$4 divisions, with differentiation probability determined with a second set of sigmoidal probability curves with midpoint Difμ_{4+} and Difμ_{8+} respectively [20,21]. Greater CD4$^+$ 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$_1$r 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$_1$R expression relative to naive S1P$_1$r expression following TC activation and with subsequent proliferation (Fig 2.F) [27–29].

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