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Physiological factors leading to a successful vaccination: A computational approach

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ABSTRACT

The immune system mounts a response to an infection by activating T cells. T cell activation occurs when dendritic cells, which have already interacted with the pathogen, scan a T cell that is cognate for (responsive to) the pathogen. This often occurs inside lymph nodes. The time it takes for this scanning event to occur, indeed the probability that it will occur at all, depends on many factors, including the rate that T cells and dendritic cells enter and leave the lymph node as well as the geometry of the lymph node and of course other cellular and molecular parameters. In this paper, we develop a hybrid stochastic-deterministic mathematical model at the tissue scale of the lymph node and simulate dendritic cells and cognate T cells to investigate the most important physiological factors leading to a successful and timely immune response after a vaccination. We use an agent-based model to describe the small population of cognate naive T cells and a partial differential equation description for the concentration of mature dendritic cells. We estimate the model parameters based on the known literature and measurements previously taken in our lab. We perform a parameter sensitivity analysis to quantify the sensitivity of the model results to the parameters. The results show that increasing T cell inflow through high endothelial venules, restricting cellular egress via the efferent lymph and increasing the total dendritic cell count by improving vaccinations are the among the most important physiological factors leading to an improved immune response. We also find that increasing the physical size of lymph nodes improves the overall likelihood that an immune response will take place but has a fairly weak effect on the response rate. The nature of dendritic cell trafficking through the LN (either passive or active transport) seems to have little effect on the overall immune response except if a change in overall egress time is observed.

1. Introduction

The immune response is the body's biological mechanism to defend against infections and comprises of both innate and adaptive immunity. While innate immunity, the first line of defence, is often sufficient to control an infection, developing essential long-term immunity requires an adaptive response. The adaptive immune response is multifaceted, however, central to the process is the activation of immune cells known as T cells.

Inactivated (or naive) T cells patrol through blood and lymphatic systems and are activated by the detection of antigen, a marker for a specific infection. T cells express receptors (TCRs) which are only specific to an associated (or cognate) antigen. T cell activation occurs when TCRs engage with a processed form of their cognate antigen known as pMHC (antigenic peptide bound to major histocompatibility complex) (Kindt et al., 2007). Efficient activation of T cells requires macrophages and dendritic cells (DCs) which express large numbers of MHC proteins. Activation causes rapid T cell proliferation and the daughter cells subsequently mount an antigen-specific response (Kindt et al., 2007).

Each T cell expresses a specific TCR and each organism needs many T cells and a wide variety of TCRs to help identify a wide range of pathogenic threats. The organism therefore has a TCR repertoire. Talking about T cells, TCRs, cognate T cells/TCRs can get confusing without a well defined language to describe them. We will use the terms defined by Laydon, Bangham and Asquith (Asquith et al., 2015). The total number of distinct TCRs which

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are created by an organism we will refer to as the TCR 'diversity' and we will use the term 'species' to describe the collection of T cells which share a common TCR (also known as clonotypes). We shall use the symbol $\mathcal{N}_{TCR}$ to describe the TCR diversity and the symbol N_t to describe the copy number of clonotypes of a given species. The copy number of clonotypes of the various species of T cell in an organism is heavily skewed but also specific to the individual. We treat N_t therefore as the effective 'average' copy number of clonotypes for each species. We can relate N_t and $\mathcal{N}_{TCR}$ therefore with the total number of T cells in the whole organism $N_{total} = \mathcal{N}_{TCR} N_t$. As an example, for the $\alpha\beta$ T cell repertoire in mice the diversity is estimated at $\mathcal{N}_{TCR} \sim 2 \times 10^6$ (Casrouge et al., 2000) whilst humans have genes which encode for a larger number of TCRs $\mathcal{N}_{TCR} \sim 2 \times 10^7$ (Naylor et al., 2005). Estimates for the total number of naive T cells in humans vary depending on the body mass and age of the individual, but are on the order of $N_{total} \sim 10^{11}$ (Bains et al., 2009) and therefore a given T cell species has approximately $N_t \sim 10,000$ clonotypes. Finding an antigen-specific naive T cell (a T cell of a specific species) amongst the total pool of T cells is like finding a needle in a haystack.

T cell activation is supported by dendritic cells (DCs). After processing antigen at the site of an infection, DCs undergo a maturation phase during which they grow long dendrites which can extend up to twice their body length (Miller et al., 2004b). Fragments of the processed antigen are displayed on MHC molecules found on the outer membrane of the DCs and the purpose of the dendrites is to interact with as many neighbouring T cells as possible, optimising the likelihood that a T cell specific to the antigen will be primed (von Andrian and Mempel, 2003; Randolph et al., 2005). For this reason, DCs are often called antigen presenting cells (APCs).

Lymph nodes (LNs) are secondary lymphoid tissues. Their main function is to facilitate the otherwise unlikely event that an antigen-specific T cell (a T cell belonging to a species cognate for the exposed antigen) will encounter its cognate antigen on a mature DC and be activated. Until the mid 2000s, theoretical studies of LNs considered them to be spatially homogeneous in which naive T cells could encounter mature DCs in a closed, concentrated environment at a rate determined only by copy number (and not spatial distribution). However, LNs are complex tissues with a spatially inhomogeneous internal structure that supports the interaction between DCs and T cells, although how this is achieved is poorly understood. A schematic cross-section of the anatomy of a LN is presented in Fig. 1. Our schematic is based on detailed diagrams presented by Willard-Mack (2006).

At the site of an infection (or vaccination), immature DCs ingest antigen, mature and are actively transported through lymphatic vessels to LNs. The lymph (the fluid in the lymphatic vessels), which carries the mature DCs, drains into a nearby LN and enters the capsule ('top') of the LN via one of the afferent lymphatic (AL) vessels (Fig. 1). Lymph that enters the LN flows into the subcapsular sinus and preferentially around the lobules, through transverse sinuses, towards the efferent lymphatic (EL) vessel where it leaves the LN. The DCs which are carried into the LN via the AL deposit on the interface between the superficial cortex and the subcapsular sinus. Scanning electron micrographs of rat LNs have revealed that the floor of the subcapsular sinus possesses pores leading to the paracortex (Ohtani and Ohtani, 2008). DCs are transported rather directly through the superficial cortex, which consists largely of follicles filled with B cells (which are not the focus of this manuscript), into the paracortex and the deep cortical unit (DCU) which contains densely packed naive T cells which are constantly being trafficked through the LNs of the organism. Two-photon experiments have provided evidence that the DCs, at a cellular level, gradually move through the cortex, in a random fashion (Grigorova et al., 2010; Miller et al., 2002). This microscopic movement is consistent with Brownian motion and diffusion constants can be calculated from experimental data (Miller et al., 2004a). However, spread throughout the DCU are sinuses carrying lymph which flows from the AL to the medulla and eventually into the EL. DCs can find these sinuses and actively move with a bias towards the EL. Therefore, it is expected that there may be some net active transport of cells from the AL to the medulla. The network of sinuses may also contribute to an increase in tissue scale dispersion of cells as well as active transport from AL to EL, but it is unclear to what extent this occurs (Murphy et al., 2007; Sainte-Marie et al., 1982). There is no evidence that mature DCs exit the LN; they are not present in efferent lymph or circulating blood and typically reside only within the LN after entering. Mature DCs in the murine LN are known to reside for an average of about 60 h (Haig et al., 1999; Neeland, 2015). It is likely DCs are triggered to apoptose (die) within the medulla and are then scavenged by resident macrophages (Tomura et al., 2014). DC fate within the LN is rather poorly understood. However, assuming DCs are removed on exiting the DCU and entering the medulla, the time spent in the LN provides us with a more reliable source of approximate transport parameters on the tissue scale than the microscopic scale transport parameters determined from 2-photon experiments.

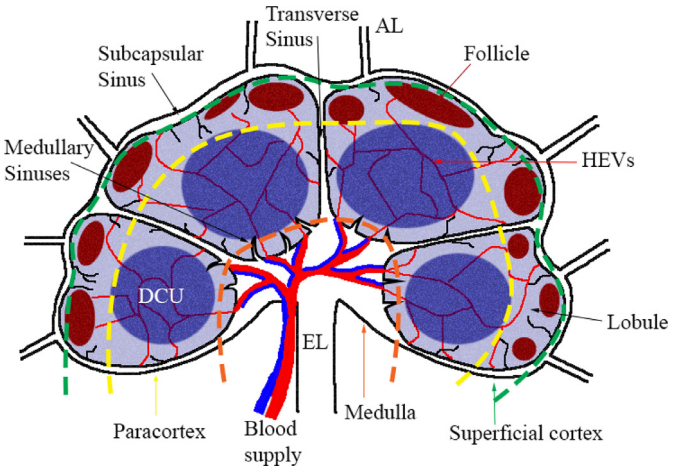

Fig. 1. Schematic cross-section of a lymph node (LN). Lymph drains DCs into the LN from nearby tissues via an afferent lymphatic (AL) vessel and then flows through the subcapsular and transverse sinuses to the efferent lymphatic (EL) vessel, whilst depositing DCs into the lobules. Lobules consist of two main regions; the superficial cortex (between green and yellow lines) typically consists of several follicles which contain B cells (maroon) and the paracortex (between yellow and orange lines), often referred to as the T cell zone because it contains mostly T cells. Within the paracortex, the deep cortical unit (DCU) contains a concentrated population of T cells (dark blue); it is in the DCU that the majority of TC-DC interactions occur. Cells from the lobules enter the medullary sinuses and are drained into the medulla (within the orange line). T cells in the medulla drain into the EL for recirculation whilst DCs are removed by macrophages. Blood supply brings T cells into the LN, where T cells are deposited into the lobules through high endothelial venules (HEVs), shown schematically in thin red lines. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Naive T cells originate from haematopoietic stem cells in the bone marrow and develop in the thymus before being distributed around the body. T cells typically enter a LN through the blood supply. The blood vessels branch into small vessels known as high endothelial venules (HEVs) that are distributed throughout the lobules in the LN. T cells in the HEVs adhere to the endothelial walls leading to transendothelial migration into the LN and particularly into the DCU (Sage and Carman, 2009). Interestingly, it has recently been shown that mature DCs can activate HEVs so that they become more permeable to T cells entering the DCU (Moussion and Girard, 2011). In the DCU tissue, T cells have also been shown to