The Physiology of Lymphocyte Migration

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***Abstract*- White blood cells (lymphocytes) are the mobile cells that make up the recognition and response component of the acquired immune system. There are pools of lymphocytes that recirculate the blood stream and the lymphatic system, there are lymphocytes that selectively home to tissues close to where the cells were created, and there are pools lymphocytes that are recruited to sites of infection and inflammation. The lymphoid tissue of the lymphatic system provides the structural scaffold for the mobility of these cells, although interestingly the migratory behaviour is controlled at the finest level – by localised chemicals and receptors on the cells themselves. This work summarises the mobility of lymphocytes providing perspectives of cell movements from the lymphatic system, movement types, cell types, and cell classes. It is believed that this review and further more detailed studies of specific aspects of cell mobility may provide a fertile basis for the design of distributed information and computation models.**

Keywords- Lymphocyte, Trafficking, Migration, Homing, Recirculation, Immunological Surveillance, Lymphatic System

I. INTRODUCTION

How do lymphocytes move around the body, and where do they move to? More importantly, what benefits does immune cell migration offer and what problems may result from such a defensive strategy?

The migration of cells involved in the immune system is highly complex and is still not completely understood. This work reviews some superficial features of lymphocyte migration in the immune system with the interest of extracting principles for use in artificial immune systems. Lymphocyte migration is reviewed in the context of the human and related mammalian (rats, mice, sheep, etc.) immune systems.

Section III introduces the anatomy of the lymphatic system that facilitates lymphocyte mobility covering the primary (II.A) and secondary (II.B) lymphoid organs. The germinal centre which is so critical to the development of B cells is discussed briefly (II.C), and the facilitating role of the system as a scaffold for cell migration is surmised (II.D). Section III provides a 'broad-stroke' summary of the complex topic of lymphocyte movement. Cell movement is addressed from the perspective of movement types (III.A) and from the perspective of cell types (III.B). In addition, the so-called 'mobile lymphocyte pool strategy' is considered both in terms of the behaviour (III.C) and in potential problems and ways of manipulating migration (III.D).

II. LYMPHATIC SYSTEM

This section provides a summary of the anatomy and physiology of the human lymphoid system relevant to the discussion of lymphocyte migration. For a more general treatment, see any current anatomy and physiology text on the subject, such as [13]. Other references used include organ summary [23] (page 71), Anderson [2], Swartz [24].

Lymph is a clear bodily fluid that surrounds all tissue. It forms when proteins and cells leak out of venules and capillaries (from the blood into tissues). The lymph carrying capillaries flows uni-directionally draining the lymph back to lymphoid tissues that make up the lymphatic system. Also carried in this lymph are antigens that may have entered the organism. The lymphatic system is a complex collection of lymphoid organs integrally related to the functioning of the immune system and responsible for the transport, filtering, and returning to the blood stream of lymph. The system acts as a secondary circulation system (to the cardiovascular circulatory system) transporting lymphocytes between lymphoid organs, and carrying antigen to lymphoid organs for interaction with lymphocytes.

There are two types of lymphoid organs (1) the central or primary tissues which are the sites of lymphocyte formation (the thymus and bone marrow), and (2) the secondary or periphery lymphoid organs where immune response take place (the spleen, lymph nodes and gut-associated lymphoid tissues). One may consider the rest of the bodies' tissues as tertiary lymphoid tissues which normally only contain few lymphoid cells, although on infection and inflammation, manage to recruit many immune cells.

A. *Primary (Central) Lymphoid Tissues*

Primary lymphoid organs consist of the thymus and the bone marrow, and are responsible for differentiating stem cells into pre-immune cells (pre-B and pre-T cells) in a process that is believed to be independent of antigenic stimulation. The bone marrow provides a microenvironment for the production of blood cells. B cells migrate to secondary lymphoid organs, where as T cells migrate to the thymus. The thymus provides an environment for the further antigen-free maturation of T lymphocytes. Cells proliferate and differentiate in a process involving negative and positive selection where the majority of produced T cells never leave the thymus.

Those cells that do survive (less than 5% per day) may join the recirculating lymphocyte pool, or migrate to secondary lymphoid tissues.

Primary Lymphoid Organs

Bone Marrow – tissue located inside large bones responsible for the production of many different blood cell types not limited to lymphocytes (white blood cells). Provides an environment for differentiation of naive B cells.

Thymus – organ located behind the sternum, provides an environment for the differentiation of naïve lymphocytes from bone marrow. These lymphocytes differentiate into T lymphocytes, which involves a negative selection maturation process.

Figure 1 - Summary of primary lymphoid organs

B. *Secondary (Peripheral) Lymphoid Tissues*

The secondary lymphoid tissue is responsible for collecting antigens at points in the organism where antigens may enter, and facilitate exposure to the collected antigen to recirculating lymphocytes. The lymph nodes are primary responsible for filtering the lymph for antigens, the spleen is responsible for filtering the blood for antigens, the tonsils for the respiratory system, etcetera (see Figure 2).

"*The central function of secondary lymphoid tissues is filtering: collecting blood-borne, lymph-borne, or mucus membrane antigens and holding these so that they can be surveyed by immune cells before being destroyed.*" [9] (page 6).

In addition, the secondary lymphoid tissue provides a suitable microenvironment for the development and maturation of an immune response, such as the formation of Germinal Centres (GC) for B cell clonal expansion and affinity maturation. These tissues are the primarily location the recognition and response to antigen.

"*Thus, secondary lymphoid organs present antigen optimally and enhance the chances of specific antigen encounter and specific cell interactions.*" […] "*…these requirements render chance encounters of antigen by lymphocytes and activation elsewhere extremely inefficient and of no biological relevance*" [27] (page 201).

Secondary Lymphoid Organs

Tonsils – collection of lymphoid tissue on the side of the throat responsible for providing lymphocyte access to and protection of the respiratory system from antigen.

Lymph Nodes – small gland like structures found throughout the body that filter the lymph for foreign antigen material, which are then presented to lymphocytes and other immune system cells.

Peyer's patches – collection of lymphoid tissue found in the lowest section of the small intestine. There are numerous instances of these patches in the intestine and they act like lymph nodes, and provide centres for lymphocytes protecting the gastrointestinal tract.

Spleen – an organ in the upper abdomen, responsible for the destruction of old red blood cells. It is the only lymphoid organ that crosses the blood stream, and thus provides a site where lymphocytes can interact with antigens carried in the blood.

Lymphatic vessels – vessels throughout the body that carry lymph. They are responsible for transporting lymph from tissues to the blood (vascular circulatory system) and to the lymph organs.

Figure 2 - Summary of the secondary lymphoid organs

The geography of the lymph nodes and other secondary lymphoid tissues plays an important structural role for lymphocyte migration [27,27,31]. Further, it is likely that the organisation and function of the secondary lymphoid organs has been optimized for recirculating lymphocytes to efficiently detect and remove pathogens from the organism.

"*…secondary lymphoid organs are thought to be organised into structures that optimize cellular interactions that support the efficient removal of unwanted pathogens*" [31] (page 400).

Finally, in addition to providing a scaffold for lymphocyte recirculation, the secondary lymphoid tissues possess a high regenerative capacity. When circulation routs are disrupted or severed, the tissue is able to adaptively regenerate a connection between the effected nodes [29]. See [28] for a review of lymph node anatomy and physiology in the context of cell migration.

C. *Germinal Centres*

Germinal Centres (Germinal Centers or GC's) are little understood dynamically generated regions in lymphoid tissue (lymph nodes) where activated B lymphocytes clonally expand, are exposed to hypermutation and ultimately differentiate into plasma (effector) and long-lived memory B lymphocytes [8][16]. GC's are founded by a small number of activated B cells (oligoclonal), which are in turn co-stimulated by helper T cells [32]. There are repeated rounds of selection, expansion, and mutation of B cells within the GC. The majority of the produced B cells may be plasma cells and have a lower affinity, although a few higher affinity clones are preferentially selected to survive as plasma or memory cells [19,25]. Those cells that are worse die due to the lack of positive selection.

Finally, it is interesting to note that GC-like structures may also occur outside of lymph nodes, such as sites of infection and allergic inflammation [17].

D.*Lymphatic Perspective of Mobility*

There are no lymphocytes or lymphocyte recirculation without the lymphatic system. The tissues are responsible for the development and management of the cells throughout their lifecycle. The following summarises the governing role of the lymphatic system for lymphocyte mobility.

Formation – Provides an optimal microenvironment for the production and maturation of lymphocytes.

Presentation – Collect diverse populations of lymphocytes into organ systems that drain antigens from entry points into the organism.

Regulation – Regulate interactions of different classes of lymphocytes in drainage organ systems, such as the arrangement of B and T cells.

Dissemination – Disburse effector elements of the immune response throughout the organism, and disseminate and amplify the immune response systematically throughout the lymphatic system.

III. Lymphocyte Movement

This section reviews lymphocyte movement from the perspective of the ways in which the various cell types are mobile. For an excellent overview of lymphocyte mobility see [2], also see [3,4,11], for a small sampling of the modelling lymphocyte recirculation see [5,7,10,12,30,33]. See Figure 3 for a summary of immunological terms related to cell mobility.

Cell movement is the basis of immunology. It is involved everywhere; inflammation, differentiation, adhesion, recruitment, and cell contact. The recirculation of lymphocytes was confirmed experimentally almost 50 years ago by Sir James Gowans and colleagues [20,21], although the study of the topic is often neglected in favour of cell interactions [1,6]. Interestingly much of the modelling work with populations of lymphocytes does not take into account the spatial heterogeneity of the lymphatic system.

The adhesion properties of cells plays a critical controlling role in the movement of lymphocytes (see Anderson for a treatment [2]). Adhesion is used by cells to crawl through tissues. It is used by activated cells to stick to the molecule that activated them. Adhesive receptors (so-called 'homing receptors') and chemicals are little understood and are a topic for intense study. The adhesive characteristics of a cell are believed to be selected for and differentiated along with cell antigenic receptor characteristics. These adhesive interactions provide bottom up control at the finest level [22] believed to be the basis for homing, recruitment and may ultimately control the extent and scope of the immune response [26].

An algorithm or series of adhesive-based decisions have to be made for a lymphocyte to be recruited into tissues, in particular from recirculation in the blood into lymphoid tissues. This process is called the multi-step extravasation or molecular regulation algorithm, which has the following four steps: (1) primary cell adhesion, (2) rapid cell activation, (3) activation dependant arrest, and (4) diapedesis, which is the movement into surrounding tissue.

Summary of terms to describe lymphocyte movement

Migration – Movement of lymphocyte cells, such as recirculation, trafficking, and homing.

Motility – (motile) the spontaneous and independent movement of a cell, usually directed movement such as down a chemical gradient. May refer to single cells or multiple cell organisms.

Chemotaxis – the directed movement of bodily cells in response to a chemical gradient in their environment. The way in which some bacteria move, also related to the directed trafficking of lymphocyte cells during their development and recruitment.

Trafficking – The directed (non-random) movement of cells from tissues, blood, or lymph. May refer to a cells trafficking route as it homes to a specific region in the body.

Homing – (localization) The directed (preferential tendency) of lymphocytes activated in a particular region of the body, to return to that part of the body. May refer to the arrival of lymphocyte to lymphoid or non-lymphoid tissue from the blood stream. Also called tissue-selective trafficking.

Recirculation – (circulation or rolling lymphocytes) The movement of lymphocyte cells around the body from lymphoid tissue, to the blood, to the lymph, and back to lymphoid tissue to repeat the process. Native and memory cells are the main recirculating lymphocyte types.

Recruitment – (sequestration) Accumulation of cells such as a site of infection or tissue damage, such accumulation may occur through chemotaxis.

Arrest – The process whereby circulating lymphocytes come to a stop (cease circulating) before entering (emigrating or homing into) lymph nodes or inflamed peripheral tissue. May also refer the stopping of a cell given its activation which results in an increased adhesion to the triggering molecule.

Extravasation – To force the flow of cells from a vessel out into surrounding tissue. Believed to be a multi-step process for lymphocytes, the result of which is recruitment into tissues.

Figure 3 - Summary of immunological terms related to lymphocyte movement

A. *Movement Types*

Physically, there are two ways lymphocyte cells can move, the first is crawling. Cells use chemical receptors to adhere to their surroundings and use this method to slowly migrate through tissues – a place where they spend most of their time given the slow pace of movement. The second mode is movement in fluid space such as in blood or lymph. Here, cells are capable of moving a lot faster, covering great distances in the organism.

The process of lymphocyte migration was originally considered to be random, although it is now known not necessarily to be the case. Lymphocytes may be preferentially recirculated, and are able home in and target specific tissues. In addition, memory lymphocytes show different migration behaviour to naïve lymphocytes.

The immune system maintains a pool of recirculating lymphocytes that cycle around the blood and the lymphatic system. The pace of recirculation is large, the number of lymphocytes entering the blood from the lymph each day is 10 times the size of the recirculating lymphocyte pool [2]. The number of lymphocytes recirculating at one time may be anywhere from 1%-2% of all lymphocytes in the body in young adult animals [1,12]. Lymphocytes may only stay in circulation in the blood for about 30 minutes.

Trepel [15] provides a seminal, although outdated extrapolation of the number and distribution of lymphocytes in man. Such numbers may be useful for a general guide, as follows: 2.2% in the circulating blood, 41.3% in the lymph node and tonsils, 15.2% in the spleen, 4.3% in the gut-associated lymphoid tissues, 10.9% in the thymus, 10.9% in the bone marrow, and about 15% in other tissues.

Memory cells, in particular memory T cells preferentially migrate to non-lymphoid tissues. For example, if a memory cell was created in a lymph node near the skin, the cell will preferentially migrate into skin tissue near the lymph node, if created in a lymph node near the gut, it will migrate to neighbouring gut tissue.

Summary of types of movement

Migrating Cells – Stem cells migrate to the primary lymphoid organs to differentiate. Pre-B cells and pre-T cells migrate to secondary lymphoid tissues to further differentiate and mature.

Recirculating Cells – Continual rolling population of lymphocytes between secondary lymphoid tissues, blood, non-lymphoid tissues, lymph, and back to the lymphoid tissues

Recruited Cells – The stopping (arrest) of recirculating cells at a point of recruitment, cells are accumulated to lymphoid tissue and to inflamed or damaged tissues.

Homing Cells – Cells with a memory of where they were differentiated may localize back to these regions.

Stationary Cells – These are cells that lodge, or do not move from the location of their differentiation. Examples include plasma B cells created in germinal centres that release large amounts of antibody.

Figure 4 - Summary of the various types of lymphocyte migration

B.*Lymphocyte Types*

There are both circulating and non-recirculating populations of B and T cells. Although the behaviours of both cell types are tightly interrelated, both have differing migration behaviours during their development and lifecycle.

Different motility of B and T lymphocytes

T lymphocytes – pre-T cells migrate to the thymus for maturation. Surviving T cells may migrate to tissues and becomes sentinel cells. Other may recirculate and seek activation in secondary lymphoid tissue. Memory T cells preferentially migrate to non-lymphoid tissues.

B lymphocytes – pre-B cells migrate from the bone marrow to secondary lymphoid tissues. Some cells will be activated by antigen in the secondary tissue and differentiate into plasma and memory cells. Other cells will be activated and migrate to the spleen before differentiating.

Figure 5 - Summary of differences in motility between B and T lymphocytes

There is commonality in the development of both B and T cells, specifically in terms of the classes of lymphocyte they may differentiate into. These include the classes: naïve, effector, and memory. Naïve cells are untested lymphocytes that seek a potential cognate antigen. Effector and memory cells result from the union of naïve cells and antigen. Effector cells, such as Helper T cells and plasma B cells remain in lymphoid tissue. Memory cells make up the majority of the recirculating pool and continue to circulate between the bloodstream and the lymphatic system, at a higher rate than naïve cells.

Migration behaviours of lymphocyte classes

Naïve Lymphocytes – Recirculate between blood and lymphoid tissue, primarily involved in responding to antigen presented in lymph nodes, differentiating into effector and memory cells. Relatively homogeneous in their recirculating behaviour. Naïve cells compete with each other for activation and contribution into the memory recirculating pool.

Effector Lymphocytes – Typically do not recirculate, stay at the site of differentiation – such as plasma B cells, which differentiate from naïve B cells in lymph nodes or the spleen.

Memory Lymphocytes – Recirculate around blood and lymphoid tissue, but also extravasate to other non-lymphoid tissues. Heterogeneous in their recirculation behaviour, restricted and selective recirculation circuits. Home to areas where they are most likely to encounter, or re-encounter their cognate antigen. The number of memory cells is maintained within a moderate range during adult life.

Figure 6 - Recirculation behaviour of some lymphocyte types

C.*Cell Mobility as a Strategy*

The anatomy and physiology of the immune system may be thought of a defence strategy for the organism, and cell mobility is an integral part of that strategy. Some resources of the immune system are fixed in position and distributed throughout the body such as lymphoid tissues, and so called sentinel T cells. Draining lymph into lymphoid tissue provides a way to localise antigen. Keeping the majority of the immune responses in movement (the detectors and effectors) provides a patrolling approach to rapidly deploy resources to wherever they are needed. To summarise, the immune system has to produce many cells to detect unknown antigen, and must collect antigen in such a way that rare detector cells are given a chance to detect them. It must a provide microenvironment for controlled proliferation and differentiation, and disperse effectors to where they are needed.

"*Nature's solution to these problems has been to compartmentalize the principle functions of the lymphoid system into discrete organs and tissues in the body, and to connect and unify these organs through the operation of an elegant system of targeted lymphocyte trafficking and recirculation.*" [22] (page 562)

One may consider a recirculating population an efficient approach in the context of alternative designs.

"*Recirculation contributes to the efficiency of peripheral immune responses by maximising stochastic probabilities of a productive meeting between antigen and its cognate T-cell receptor.*" [18] (page 161).

This strategy may be considered to have the following general properties:

Movement – Different cells and cell types have differentiated migration potentials (so called 'differential migration'). Lymphatic system provides a pathway, which allows lymphocytes to recirculate between blood, peripheral tissues, and lymph nodes.

Balance – The so-called stirring or mixing effect of the recirculating lymphocyte pool facilitates the survival of the fittest – that is the survival of the most appropriate clones in the repertoire. The segregation in the repertoire prevents competition between unrelated lymphocyte subsets. Tissues selectively facilitate the segregation of lymphocytes to where they are needed. Such a balance between recirculation and homing may be critical to lymphocyte homeostasis [14].

Coverage – A repertoire of cells is distributed and rotated in an attempt to expose rare (specialised) cells to as many opportunities for activation as are available. This may be considered the maximisation of coverage, where the rolling population seeks to maximise the probability of specialised cells being exposed to their cognate antigen. Large-scale migration allows a wide repertoire of specific lymphocytes to exist at a very low frequency, yet still function efficiently.

An example of this is T cells. Perhaps 1 in 10,000 T cells released form the thymus will have a receptor that can detect a given antigen. This means that statistically at least 10K cells must hit an antigen before the right one does [2].

Surveillance – Lymphocytes may be thought of as patrolling the organism, seeking cognate antigen or recruitment. They may also thought of as monitoring the organism for change to self – for self antigen such as tumours in what is known as 'immunosurveillance'.

Amplification – Recirculation permits recruitment, the dynamic reallocation (localisation) of specialised resources to locations where they are needed. Further, system is capable of further specialising the recruited resource and disseminating that information

Dissemination – The pathway provided by the lymphatic system provides a highway to rapidly distribute information such as the immune effector cells, antibodies, and long lived lymphocyte cells that retain a refined memory of an antigenic exposure for a future rapid response.

Alternative – It provides a distributed mobile defence strategy and is different to other subsystems of the body such as the nervous system, which is distributed but structurally fixed. Further, if the repertoire did not recirculate then each lymph node would be an isolated (island) repertoire. Thus, each such isolated repertoire would either have to be as large as the entire recirculating pool, or a smaller pool resulting in less antigenic coverage.

D.*Problems and Changes to Migration*

The rate and nature of lymphocyte migration does not remain constant, and in fact it may be desirable is certain circumstance to manipulate the recirculation behaviour of lymphocytes. Alternatively, the very recirculating behaviour of lymphocytes that provides a dynamic defence may also facilitate significant problems for the host organism.

During an immune response, the lymph nodes may rapidly recruit cells from blood, temporally blocking them from leaving the tissue. This in addition to clonal expansion causes the nodes to swell in size and become store. This swelling of the glands is a common sign of illness. It highlights the point that when an antigenic stimulus is detected by the immune system, it has a profound effect on the entire system affecting production and circulation behaviour of lymphocytes.

There are some diseases that disrupt and decrease the migration and homeostasis of lymphocytes [3], thus it may be desirable to increase cell migration. Some approaches may include increasing blood flow, increasing the expression of adhesive chemicals, and manipulating the tissues where immune responses take place. Alternatively, there are diseases where it is desirable to decrease the recirculation of lymphocytes. Examples include when tissues are transplanted, and autoimmune diseases. In both cases the immune cells seek to destroy health tissue, thus strategies focus on affecting the recruitment of cells to these areas.

The lymphatic system may facilitate the spread of disease in the body. For example, cancers and tumour cells are able to spread quickly throughout the lymph nodes of a host. Bacteria can use the lymphatic system to disseminate throughout the body. An example mentioned in [28] is the bacteria 'Yersinia pestis' so called the most devastating bacterial pathogen in human history (the cause of the bubonic plague). It manages to get in to tissue through flee bites and moves to the lymphatic system where it proliferates, quickly overwhelming lymph nodes and spreading throughout the body. Other examples include HIV, mycobacteria, anthrax.

IV. Discussion

As stated, lymphocyte migration is crucial to the functioning of the immune system, and the study of the complexities behind circulation, homing, and recruitment remain an active area for research. This work provided a high-level summary of the physiology of lymphocyte migration, although it glossed over many of the subtle and intricate details involved.

Some topics that may deserve their own treatment include: (1) the Germinal Centre (GC) in secondary lymphoid tissue, (2) the role of Dendritic Cells (DC) in lymphoid tissue for antigen presentation, (3) adhesion molecules 'homing receptors' and their role in recruitment with regard to endothelial venules (where lymphocytes leave the blood), (4) sentinel T cells that await the arrival of antigen near skin tissue, and finally (5) immunological surveillance 'immunosurveillance' of tissues for cancer cells.

A goal of this work was to broadly describe lymphocyte migration such that the principles may inspired the design of information processing and computational models. Section III.C described lymphocyte distribution and mobility as a defence strategy, and it is believed that the properties listed in that section provide a suitable base for this purpose. Specifically the aspects of a recirculation-segregation trade-off, immune surveillance, and information dissemination provide a fertile basis. In addition, the architectural scaffold of the lymphatic system, the lymph nodes in particular, combined with the generic treatment of cells (B/T or cell classes) are likely to provide useful abstractions for distributed system design. Employing these principles in the design of information processing models remains an exercise for future work.

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