OPINION

T cell migration, search strategies and mechanisms

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Abstract | T cell migration is essential for T cell responses; it allows for the detection of cognate antigen at the surface of antigen-presenting cells and for interactions with other cells involved in the immune response. Although appearing random, growing evidence suggests that T cell motility patterns are strategic and governed by mechanisms that are optimized for both the activation stage of the cell and for environment-specific cues. In this Opinion article, we discuss how the combined effects of T cell-intrinsic and -extrinsic forces influence T cell motility patterns in the context of highly complex tissues that are filled with other cells involved in parallel motility. In particular, we examine how insights from 'search theory' can be used to describe T cell movement across an 'exploitation–exploration trade-off' in the context of activation versus effector function and lymph nodes versus peripheral tissues.

Every T cell expresses a specific T cell receptor (TCR), which can recognize a limited range of peptide–MHC complexes on the surface of antigen-presenting cells (APCs). As a consequence, about one T cell in 10^5–10^6 T cells is specific for a given antigen, referred to as its cognate antigen[1–3]. During an immune response, a T cell has to encounter its cognate antigen many times in different contexts and tissues.

The varying requirements for T cells to move and to recognize their cognate antigen on APCs and other targets can be best appreciated across the lifetime of an immune response, as it shifts from lymphoid organs to target organs. The initial encounter between naive T cells and their cognate antigen usually happens in secondary lymphoid organs, including lymph nodes. Lymph nodes are highly organized organs that provide a confined and structured architecture to facilitate T cell scanning of potential APCs, especially dendritic cells (DCs) coming from different tissues[4]. As naive T cells, by definition, have not yet encountered their antigen, they are all generic and lack information about their need to participate in a response. By contrast, recently activated T cells upregulate mechanisms and receptors that modify their migration patterns to follow or find cognate APCs and other recently activated immune cells; these additional mechanisms allow them to find and reside within an inflammatory microenvironment in the lymph node to undergo and induce full differentiation. Most differentiated effector T cells then leave the lymph nodes and migrate to and scan peripheral tissues to once again find their antigen[5]: this antigen re-encounter results in killing of infected host cells by effector T cells and the maintenance of T cell effector functions[6].

The principal purpose of T cell motility is to 'search' for cognate antigen on APCs and for target cells. The process of search is a fundamental requirement in almost any biological system in which many agents (that is, cells and organisms) reside within an ecosystem much larger than their perceptual capabilities. T cells fit this criterion, and this article builds upon search theories originating from other fields, including ecology, to describe T cell behaviour across different tissues.

Because the immune response must quickly detect and respond to antigen stimulation to eradicate pathogens and tumour cells, T cell activation requires rapid scanning of as many APCs as possible. However, T cells must balance migration speed with the need to dwell in a given location for long enough for the TCR and peptide–MHC complex to engage and transmit an activating signal to the T cell. Motility patterns undertaken by T cells should probably resolve, in different contexts and by different mechanisms, the classic 'exploitation–exploration trade-off' (REF. 7) (BOX 1). In essence, to be most efficient, T cells must balance motility strategies that exploit available information such as that conveyed through integrins, chemokines and peptide–MHC complexes (that is, information that provides 'expectations' to determine where to move) with strategies that allow for exploration for new information (that is, sampling the environment, typically without a high level of sensory instruction).

As with many biological movements[8], T cell motility was initially characterized as resembling a random walk[9] (BOX 1), which is defined by stochastic movements with trajectories that consist of successive randomly oriented steps. In random walk theory, the rate of cell movement away from a point of origin can be described using a diffusion model[8]. Two different types of random migration have been used to model T cell motility: diffusive (Brownian-type) random walks[10] and superdiffusive (Lévy-type) random walks[11]. When pauses drive the overall movement, subdiffusive patterns may also be observed[12] (BOX 1). In addition, under some circumstances and for short times, T cells can undergo fully ballistic migration (that is, in a nearly straight line)[13].

This range of T cell motility is generated by a combination of cell-intrinsic locomotion events (for example, those controlled by rates of actin polymerization and location of cortex contraction), physical guidance cues from the microenvironment (for example, cues provided by collagen fibres and the orientation of stromal cells) and chemical information provided by the microenvironment (for example, chemokines, antigen dose and through co-stimulatory molecules). The requirement and relative importance of each parameter varies between tissues and is dictated by many factors such as the activation status

of the T cell, the density of the cognate APCs and the organization of the stromal environment. This can result in radically different motion patterns in various tissues, with consequences for the global search efficiency. In this article, we explore how coordination between the properties of the tissue microenvironment, the information provided by other cells, such as other T cells and APCs, and the cell-intrinsic motility behaviour of T cells may optimize search processes and therefore immune responses.

T cell search in lymph nodes

One of the most efficient strategies to find a prey in a simplistic system is to detect the location of the prey and undertake ballistic migration towards it[14]. However, this behaviour is not typically observed during naive T cell search in lymph nodes. An intuitive reason for this is that T cells cannot know that their cognate antigen is being presented by a given APC in order to move towards it. Because the fraction of naive T cells that are specific for any antigen is extremely small[1], the best search strategy is one that provides a relatively equal chance for all T cell clones to scan a given APC. By contrast, unselective recruitment leading to directional movement of many unrelated T cell clones towards an incoming APC might create a bottleneck. We therefore argue here that a naive T cell search strategy in lymph nodes is initially information-poor and exploration-based. Additionally, physical barriers to APC access that are introduced by endothelium, stroma or other cells may also be responsible for the apparent random migration of naive T cells in lymph nodes.

A final consideration for T cell motility strategies is the latency that exists between antigen encounter and actual T cell activation. Although T cells are apparently sensitive to single peptide–MHC complexes when they are presented in a dish, T cells typically have to stay in contact with the APC for at least a minute to be primed[15,16]. Therefore, T cell motility strategies are not necessarily efficient per se but are adapted to the complexity of the system — that is, the combined need to touch an APC and dwell long enough for TCR signalling to be initiated.

Naive T cells: non-informed motion. Within the T cell zone of lymph nodes, naive T cells display features of a diffusive (Brownian-type) or subdiffusive random walk[9,17–20] (FIG. 1a) but also show speed fluctuations, alternating between periods of fast and slow locomotion[21,22]. Ecological studies show that speed fluctuations broadly alter overall diffusive properties and search efficiency[23,24]. Based on computer simulations, it was first hypothesized that speed fluctuations in lymph nodes could be the consequence of the heterogeneity of the microenvironment or of the presence of obstacles[25]. Although T cells[26] and other immune cells[27] do not require integrins to efficiently move in lymph nodes, empirical evidence suggests that speed fluctuations are partially linked to integrins. Bursts of high speed observed during naive T cell motility are mediated by lymphocyte function-associated antigen 1 (LFA1; also known as αLβ2 integrin) on T cells interacting with intercellular adhesion molecule 1 (ICAM1) expressed on DCs[28]. Alternatively, it has recently been shown that speed fluctuations could be linked to heterogeneous T cell movements, for which persistent and diffusive random walk behaviours coexist[29].

It has also been proposed that the random walk of naive T cells is supported by a network of fibroblast reticular cells (FRCs)[30,31],

Box 1 | Search theory

Relationship between motility and search

Biological systems (ranging from cells to animals) use and react to sensory information they receive as they move[109]. In addition, relevant information can be stored and used to generate effective movement[110]. Expectation relies on the quality and nature of prior information given by the environment and, depending on such information, active search behaviour might alternate between capitalizing on high-quality information and moving some distance away to discover new information[72]. In the field of behavioural ecology, an outstanding question is whether, at the landscape level, movement patterns are due to exploratory behaviour (less-informed movement) or navigation (informed movement) or are simply due to the summation of locally reactive movement behaviour (for example, taxis)[111,112]. Similarly, there is not much appreciation of what governs the exploitative and exploratory behaviours that result in T cell search migration patterns.

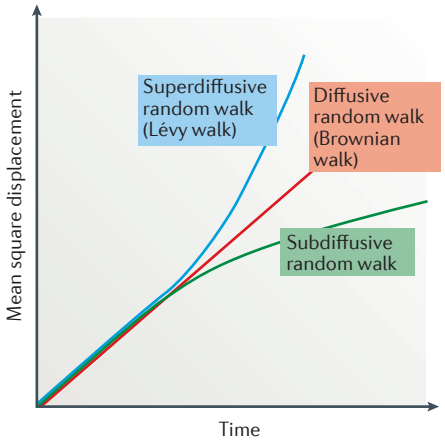
Search theory posits two main theories to explain how search processes are optimized: one, have good prior knowledge (expectations) about target locations; and two, adjust exploratory movement behaviour to elementary search rules that are less reliant on cues from the environment or prior knowledge. Therefore, speed fluctuation and turning behaviour are tuned to the environment through two elementary search trade-offs[87]: the balance between speeding-up to cover larger areas and remaining slow enough to keep perception at high performance — the so-called speed–perception trade-off[23,24,113] — and the balance between thorough local exploration and the capability to spread out to new and distant areas — the so-called intensive–extensive trade-off[24,39].

Exploration–exploitation trade-off

Exploration–exploitation trade-off is a classic decision-making trade-off based on the amount of information available on prey location. Exploitative behaviours are based on ready-to-use information, whereas explorative behaviours are aimed at looking for new information without much guidance cues. In spatial searches, exploitative behaviours are typically associated with intensive, local search, whereas explorative behaviour are associated with extensive (highly directional or ballistic) search, although new search theories are starting to challenge this concept (see above and REFS 23,24,114).

Diffusive random walks. These are random walks with no directional persistence or short-ranged (fast decaying) persistence, such that the overall spreading (that is, mean square displacement) is linear with time (see the figure). Brownian motion is the limiting case of diffusive random walk.

Anomalous dynamics: subdiffusive and superdiffusive random walks. Generalized random walks with sublinear (subdiffusion) or superlinear (superdiffusion) spreading (that is, mean square displacement) with time (see the figure). Microscopic mechanisms involved in such motility patterns include speed fluctuations. The typical example of a superdiffusive walk is the Lévy walk, which is a mix of long trajectories with finite speed and short random turning directions between move lengths[87,88]. Lévy walks (and similar types of movement)[115] are effective at randomly encountering both nearby and far-away targets[85,87,88,95], because they ensure a good local space-filling migration strategy and, at the same time, a superlinear spreading that reduces the time needed to reach distant areas. However, Lévy walk patterns could emerge not only from an explorative process but also from informed movement and its interaction with the environment.



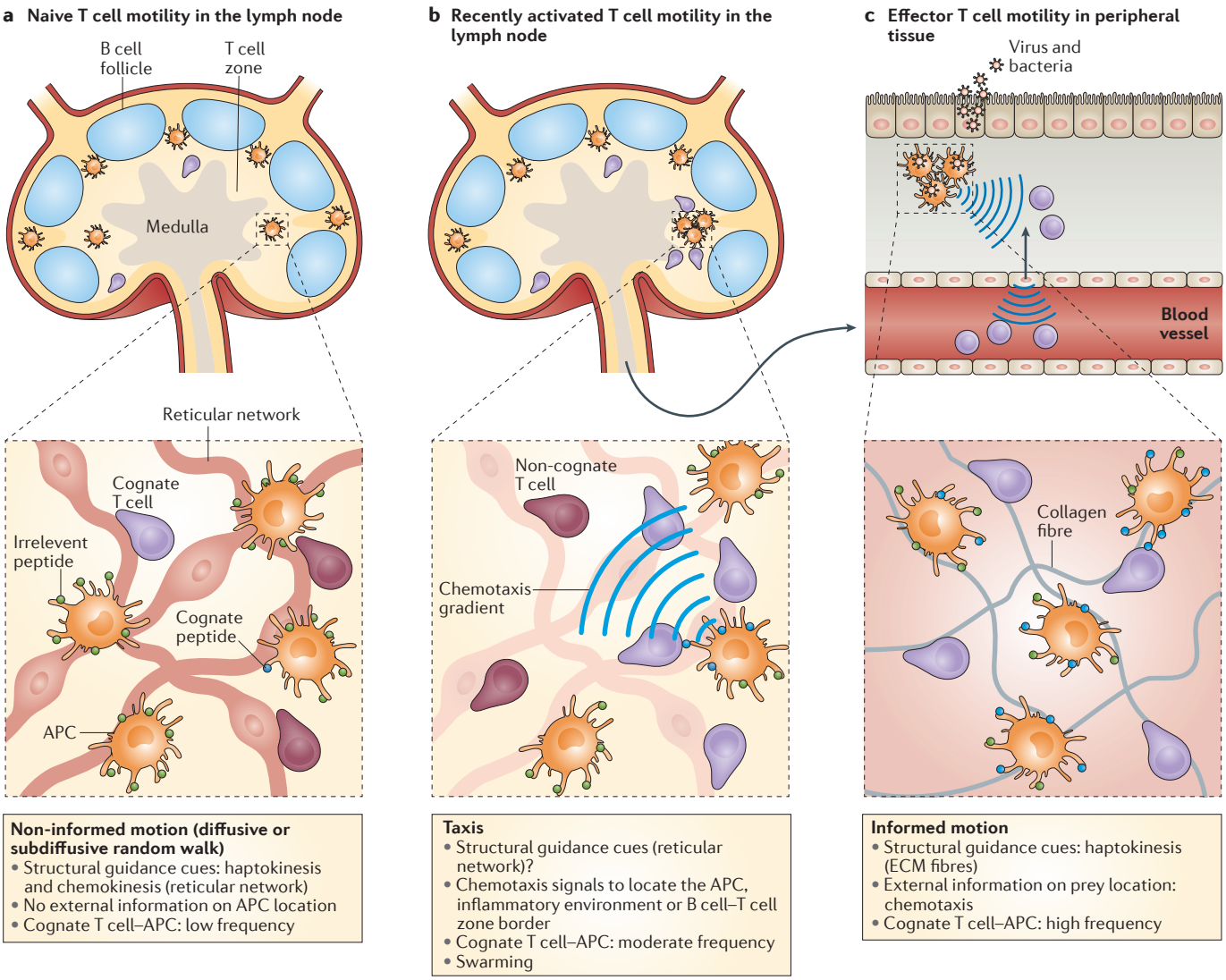


Figure 1 | **T cell motility according to its state of activation and the microenvironment. a** | Naive T cells migrate primarily in lymphoid organs, looking for their cognate peptide (in blue) presented by an antigen-presenting cell (APC). The frequency of cognate APCs in the pool of presenting cells in the lymph node is extremely low, and there is no external information to help the T cell locate the cognate APC. Naive T cells in lymph nodes use a diffusive (Brownian-type) or subdiffusive random walk. Naive T cell migration is in part cell-autonomous, supported by guiding stromal structures and relies on haptokinesis and chemokinesis. **b** | Recently activated T cells are preferentially located in a differentiation microenvironment in the secondary lymphoid organ in which they were primed. This relocation is controlled by a secondary T cell–APC interaction, which, in addition to other interactions (not shown), allow $CD4^+$ and $CD8^+$ T cells to come close to each other and form clusters, favouring $CD8^+$ T cell memory differentiation. T cell migration to this microenvironment is now directionally biased. Chemotaxis signals are produced by the cognate APC, most probably to attract recently activated T cells to a distinct differentiating environment, resulting in migration patterns governed by taxis. **c** | Once primed, T cells efficiently differentiate into effector T cells, they leave secondary lymphoid organs and are recruited by chemotaxis gradients to the site of injury in peripheral tissues. In this tissue, effector T cells have to find their cognate APC again during antigen re-encounter. Depending on the tissue and the type of injury, effector T cell migration in peripheral sites has been described as a diffusive (Brownian-type) or superdiffusive (Lévy-type) random walk. Haptokinesis and chemotaxis have been shown to shape this walk in some tissues such as the skin. ECM, extracellular matrix.

leading to the description of 'guided random walk' (REF. 32). FRCs express the chemoattractants CC-chemokine ligand 19 (CCL19), CCL21 and CXC-chemokine ligand 12 (CXCL12)[33,34], which are required for optimal naive T cell motility *in vivo*[26,31,33,35], consistent with a model of chemokinesis. Lysophosphatidic acid (LPA), another chemoattractant produced by stromal cells, has also recently been implicated in T cell motility in lymph nodes: interstitial T cell migration is reduced when LPA production is inhibited[36], further supporting the notion that naive T cells undergo chemokinesis. In some areas of the lymph node, the space between FRC fibres is large enough to accommodate many T cells, suggesting that some T cells do not contact FRC fibres. Thus, while some cells may be 'guided' by FRCs, others probably 'push off' of one another to migrate.

Cues from the microenvironment seem to have minimal impact on the directionality of naive T cell migration in lymph nodes. Chemokines present in the lymph node increase basal T cell motility — through haptokinesis or chemokinesis — but they do not appear to contribute to search strategies undertaken by T cells at the initiation of a response. For instance, although CC-chemokine receptor 7 (CCR7), the

receptor for CCL19 and CCL21, is required on T cells for maintaining their average speed, it does not control other features of the random walk, including directionality[12]. Furthermore, computational analysis suggests that the density of the FRC network has limited impact on the probability of a naive T cells finding rare cognate antigen[37].

Speed fluctuations in naive T cell motility are also intrinsically programmed[21]. In studying the cytoskeleton protein myosin 1G (MYO1G) in T cells, we recently demonstrated that T cell-intrinsic reorientation or turning patterns, along with intrinsic speed regulation, contribute to search[38]. MYO1G increases the frequency and extent of T cell turning and decreases speed and directional persistence. With respect to search efficiency, both *in silico* modelling and empirical data show that, although MYO1G-deficient T cells cover territory more quickly, the detection of rare antigens is impaired[38]. This deficit corresponds to a decreased dwell time on each APC visited and suggests that poor detection results from an inefficient exploration strategy. Because MYO1G is not required for chemotaxis or adhesion to integrins, this suggests that speed fluctuations and turning patterns are intrinsically tuned to adjust the fundamental speed–perception and intensive–extensive search trade-offs (BOX 1), as it has been similarly defined in some behavioural studies[24,39]. In effect, this study demonstrates that naive T cells are intrinsically tuned for search[38].

One key question is how MYO1G activity may be regulated, at the transcriptional level or at the protein level, so as to tune ballistic versus intensive search. Moreover, as we move beyond this finding, it is generally important to consider how cells tune their intrinsic motility on the basis of their function. For example, $CD4^+$ T cells scan a greater number of DCs per unit of time in lymph nodes compared with $CD8^+$ T cells[40], suggesting that $CD4^+$ T cell motility may be 'tuned' to scan more APCs but less thoroughly than $CD8^+$ T cells. At present, the source and reason for this difference remain unresolved.

It should also be emphasized that T cell search strategies seem to take advantage of many 'prey', and T cells frequently engage in motile synaptic interactions with different APCs. This may permit them to home in on the 'best' APC or to convert to a 'swarm', as discussed below. Serial T cell–APC encounters[41] also allow T cells to collect a series of short signals from different APCs until a critical activation threshold is achieved[42]. This might be especially relevant for T cells that have a low affinity for their cognate peptide. Whereas a high affinity for cognate peptide induces T cell arrest and stable T cell–APC interactions, weak-affinity peptides induce a switch of migration mode characterized by partial deceleration and frequent direction changes[43]. This would be expected to favour local exploitation so as to accumulate more TCR signalling.

To conclude, because naive T cells cannot specifically sense the location of their cognate antigen, they constantly alternate between exploration and exploitation modes to balance the need to visit as many potential APCs as possible while scanning each cell long enough to successfully detect their cognate antigen.

Recently activated T cells: increased expectation and informed motion. Once naive T cells find their cognate antigen and an immune response is initiated, activated T cells have to find and reside within the inflammatory microenvironment to fully differentiate into effector or memory T cell subsets. The exact composition of this 'differentiating' microenvironment is not fully understood, but it is well established that $CD8^+$ T cells require a combination of inflammatory signals[44,45], 'licensing' by APCs and $CD4^+$ T cell help for their differentiation[46]. It has recently been observed that APCs themselves undergo migration and, ultimately, aggregate in the interfollicular region of lymph nodes together with recently activated $CD4^+$ T cells and $CD8^+$ T cells[47–50], suggesting that APCs might guide the relocation of T cells to the differentiating microenvironment[48]. It has also been shown that recently activated T cells upregulate a variety of chemokine receptors[51,52] and thereby acquire sensitivity for additional chemoattractant cues. Concomitantly, FRCs gradually downregulate the expression of the homeostatic chemokines CCL19 and CCL21 after the initiation of the immune response[33,53]. As a result, T cell motility patterns shift from a diffusive (or subdiffusive) random walk towards environmentally guided migration (that is, they have increased 'expectation') (BOX 1; FIG. 1b).

One of the first pieces of evidence showing that T cells are 'guided' to a differentiating microenvironment by APCs was provided by the discovery that APCs interacting with $CD4^+$ helper T cells can attract $CD8^+$ T cells[54]. Recently activated, but not naive, $CD8^+$ T cells upregulate CCR5 (REFS 54,55), enabling them to respond to CCL3 and CCL4, which are produced, among others, by APCs[56], and receive help from $CD4^+$ T cells[54]. DCs expressing XC-chemokine receptor 1 (XCR1) have also been recently described as the DC subset that brings $CD4^+$ T cells and $CD8^+$ T cells into close proximity in the context of viral infection[57,58]. Interestingly, T cells secrete the XCR1 ligand XCL1 soon after activation[59]. XCL1 has been shown to attract DCs and regulate T cell effector function *in vitro*[60,61]. Although the mechanism by which the XCR1–XCL1 axis may control DC and T cell migration remains to be established, it is tempting to speculate that XCL1 reinforces co-migration and coalescence of recently activated T cells and APCs.

CXCL9 also attracts recently activated T cells, particularly in the spleen where it favours the commitment of $CD8^+$ T cells to a terminal effector phenotype[62,63]. Expression of the receptor for CXCL9, CXC-chemokine receptor 3 (CXCR3), on activated $CD8^+$ T cells preferentially promotes their recruitment to the marginal zone where CXCL9 is expressed by DCs and macrophages[63,64]. This suggests that CXCL9 drives the localization of activated $CXCR3^+CD8^+$ T cells to a distinct microenvironment that favours their commitment to effector $CD8^+$ T cells as opposed to memory $CD8^+$ T cells.

Finally, a change in the chemokine balance following the initiation of an immune response has been shown to promote the encounter of T cells with B cells to help B cell differentiation without disrupting the overall lymph node architecture. After priming, a subset of $CD4^+$ T cells transiently increases CXCR5 expression while decreasing CCR7 ligand responsiveness, allowing them to move towards B cell follicles where the ligand for CXCR5, CXCL13, is expressed[65].

Glossary

Chemokinesis
Migration driven by soluble chemokines, without any cue gradient to provide a directional bias.

Haptokinesis
Migration along a surface, utilizing immobilized ligands such as chemokines or integrins, without any cue gradient to provide a directional bias.

Chemotaxis
Migration driven by a gradient of soluble chemokines, which occurs when an asymmetry in chemoattractant (such as rate and density) exists and local cue gradients can be followed.

Haptotaxis
Migration along a surface that is guided by a gradient of immobilized chemoattractants or adhesion receptor ligands, which provides a directional bias.

Concomitantly, activated B cells transiently increase their expression of CCR7 (REF. 66). This coordinated response results in efficient T cell–B cell encounters at the edge of follicles where B cells receive $CD4^+$ T cell help.

Overall, current data support the model in which recently activated T cells shift towards an 'exploitative' motility pattern that is driven by chemotaxis, allowing them to sense information that is encoded by other cells involved in the immune response to relocate to an inflammatory microenvironment. In this context, in addition to T cells searching for APCs, we need to consider that APCs are also searching for cognate T cells. This is particularly apparent at the border of the T cell and B cell zones where activated B cells and T cells both migrate towards one another[67]. Furthermore, concomitant searches by each individual cell, generating an information-rich environment that is ripe for exploitation behaviour, are likely to be the source of 'swarms' of recently activated T cells around APCs that are observed in lymph nodes after initial antigen recognition[68]. Swarming behaviour is probably important for sharing cytokines and tuning effector T cell differentiation, as well as providing a niche for T cell proliferation. As we study swarms in future, it may be useful to think of them as 'linked' searches, in which each cell is simultaneously a predator and a prey.

Central memory T cells: informed motion. Memory T cells are long-lived cells generated after an infection or injury and have features that allow rapid responses upon a secondary exposure to an antigen[69]. Unlike naive T cells, memory $CD8^+$ T cells do not reside in the deep paracortex of lymph nodes but are mostly found beneath B cell follicles, close to high endothelial venules, and are therefore strategically positioned to rapidly encounter cells infected by pathogens that are circulating in the lymphatics[70]. Furthermore, memory T cells are efficient at detecting and responding to viral antigen in peripheral areas of lymph nodes, which are poorly accessible to naive T cells, within the first few hours of viral infection[71]. This accelerated detection of antigen by memory T cells is guided by a coordinated cascade of cytokines and chemokines. Memory T cells residing at the periphery of a lymph node undergo rapid arrest on infected cells and secrete interferon-γ (IFNγ), which induces CXCL9 expression from local myeloid and stromal cells. CXCL9 acts in a feedforward loop to amplify the response by recruiting more $CXCR3^+$ memory $CD8^+$ T cells to the infected region[70,71].

Different T cell subsets (here, naive and memory T cells) that are migrating in the same environment respond differently to the same cues, reinforcing the notion that the environment is not the sole driver of search patterns. Ecological behaviour studies show that animal search is influenced by the quality and nature of previous encounters and the information received from the environment[72]. For memory T cells, expectation is triggered by the previous encounter with cognate antigen, which results in their localization to sites where infection is likely to first appear and allows for their rapid recruitment upon secondary infection.

To conclude, T cell search patterns in lymph nodes are strongly influenced by the activation state and differentiation status of the T cell (FIG. 1). Whereas naive T cells do not rely on extrinsic information to find their cognate antigen, recently activated and memory T cells have increased expectation that is triggered by previous antigen encounter. Specifically, recently activated T cells respond to chemotaxis to sense other cells recruited to the immune response. Finally, strategic positioning and an increased response to chemotaxis allow rapid recruitment of memory T cells.

Effector T cell search in peripheral tissues

Following differentiation, T cells acquire the capacity to produce effector cytokines and leave the lymph nodes. Through the expression of specific tissue-homing receptors, these cells then access peripheral tissues, with the goal of eliminating invading pathogens and/or tumour cells. The mechanisms controlling effector T cell recruitment to tissues, which have been extensively reviewed elsewhere (see REFS 73–75) and are not addressed here, would clearly correspond to a cue-guided motility event (FIG. 1c).

After effector T cells enter an inflamed peripheral tissue, effector functions are induced by either antigen-dependent or -independent stimuli (for example, cytokines)[76]. In the case of antigen-driven reactivation, effector T cells have to once again find their cognate peptide. In a mouse model of breast cancer, $CD103^+$ DCs were found in close proximity to effector $CD8^+$ T cells — that is cytotoxic T lymphocytes (CTLs) — at the tumour site and were shown to reactivate antigen-specific T cells[77], which is required to maintain their cytotoxic functions[78,79]. Similarly, CTLs were shown to interact with DCs in the pancreas during type 1 diabetes[80], and this interaction was necessary for optimal CTL effector functions and disease progression[81]. $CD4^+$ T cells also need to re-encounter antigen in tissues to induce their effector functions. In the lungs of mice with allergic inflammation, $CD4^+$ T cells form conjugates with lung-resident DCs, resulting in TCR signalling[82]. Furthermore, antigen-specific $CD4^+$ T cells present in the skin during a contact hypersensitivity reaction exhibited reduced velocity and high production of IFNγ immediately after TCR engagement[83,84], consistent with a role for antigen re-encounter in maintaining T cell effector functions.

Stimulation of effector T cells in peripheral tissues has different requirements compared with naive T cell priming in lymph nodes, and this probably results in a different exploitation–exploration trade-off in effector T cells. First, the frequency of T cell–APC encounters in the inflamed tissue is presumed to be much higher than in lymph nodes, as most of T cells recruited to the inflamed site are antigen specific. Second, unlike naive T cells, co-stimulation is not strictly necessary for effector T cell activation[79], suggesting that effector T cells might not have to dwell on an APC as long as naive T cells to become activated.

Migration in the skin. Most peripheral tissues are characterized by a dense extracellular matrix (ECM) network, and changes in it result in changes in T cell search behaviours in the skin. Inflammatory mediators, in particular transforming growth factor-β (TGFβ), tumour necrosis factor (TNF) and IFNγ, increase protease secretion and ECM turnover[85] and, in a mouse model of complete Freund adjuvant-induced dermal inflammation, the ECM network loosens[83]. This loose network results in αV integrin-dependent T cell migration[83], which contrasts with T cell migration in the lymph nodes where integrin adherence is dispensable. This haptokinetic motility commonly occurs on mesenchymal cells[86]. T cell haptokinesis also probably occurs in the diabetic pancreas and in the lungs during influenza virus infection, as infiltrating T cells have been shown to express a high level of collagen-binding integrins[83,87–89], which suggests a requirement for immobilized ligands for migration.

The local environment in the inflamed skin also results in the aggregation of antigen in a common location, leading to more efficient search, providing that T cells can follow chemotactic cues to these depots. Indeed, a recent study has shown that during contact hypersensitivity, CXCL2 production by macrophages attracts dermal APCs, which

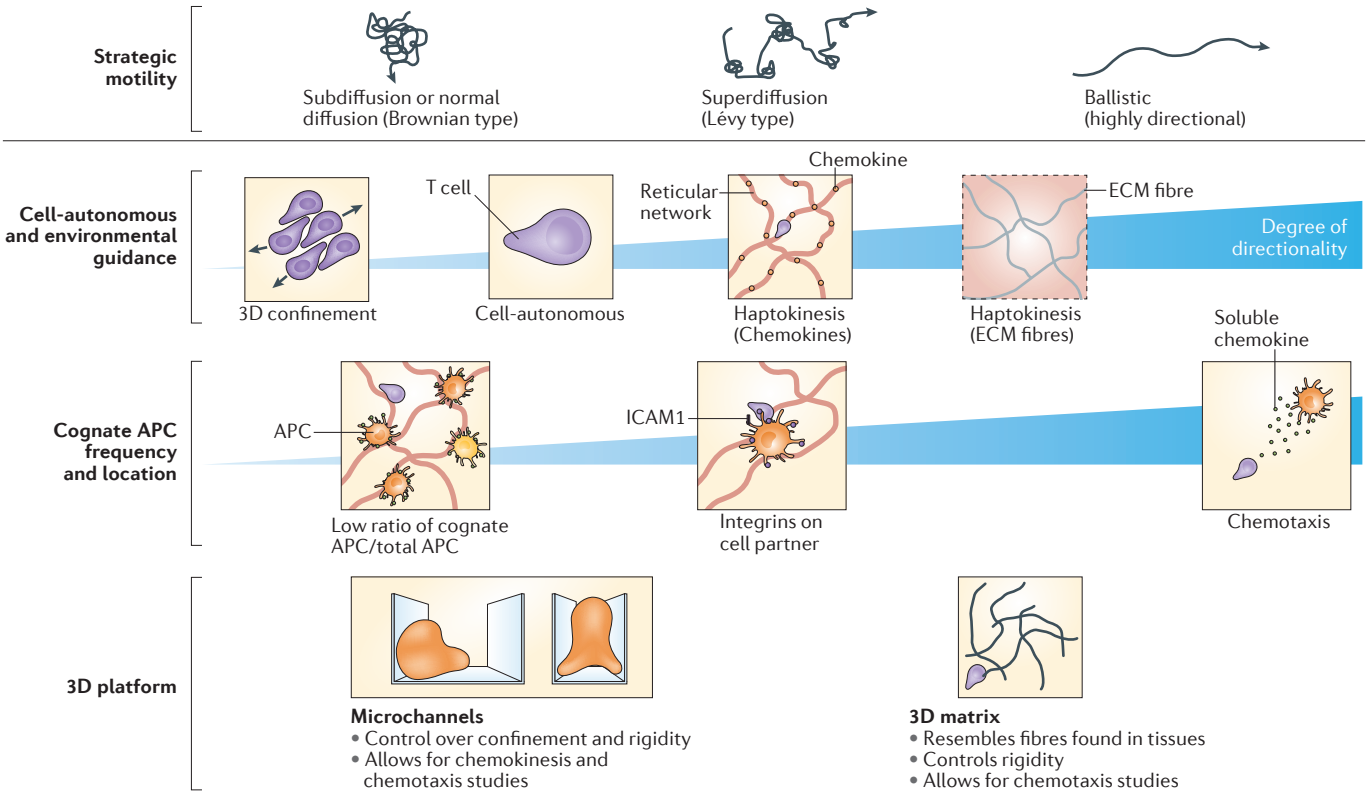


Figure 2 | **Factors influencing the features of T cell motility and platforms used to study T cell migration characteristics.** The different types of T cell strategic motility behaviours range from Brownian-type normal diffusion (top left) to highly directional ballistic (top right), passing through Lévy-type superdiffusive regimes (top middle). Different factors are known to dictate these behaviours. Strategic motility is influenced by environmental guidance structures, such as 3D cell confinement, which is required for naive T cell basal random motility, and by cell-autonomous features, such as those controlled by myosin 1G (not shown). Cell-autonomous mechanisms and haptokinesis driven by chemokines are involved in subdiffusion to superdiffusion motility patterns. Haptokinesis on extracellular matrix (ECM) fibres in tissues such as the skin and brain is involved in more ballistic, directional migration patterns of effector T cells. Strategic motility is also influenced by the frequency and location of the cognate antigen-presenting cell (APC). In particular, a low ratio of cognate APC/total APC is associated with subdiffusive migration patterns. Integrins such as intercellular adhesion molecule 1 (ICAM1) expressed by cell partners, mainly APCs, locally increase T cell speed, resulting in speed fluctuations that can be seen in superdiffusive patterns. Chemotactic signals sent by the cognate APC attract activated T cells, promoting directional T cell migration. Finally, different platforms can be used to study specific migration parameters of T cells. Microchannels allow for the study of cell-autonomous migration, confinement, chemokinesis and/or chemotaxis. 3D matrices resemble fibres found in tissues and allow control over rigidity and chemotaxis studies.

form clusters[90]. Effector T cells have to join these clusters to proliferate and produce cytokines[90]. Whether APCs actively attract effector T cells in this context is unclear, but similar migration patterns and aggregation of DCs are observed in lymph nodes where they probably contribute to a highly localized immune reaction[47,48].

Additional evidence supports the concept that the environment provides enhanced motility cues to optimize antigen discovery by effector T cells. In a mouse model of epicutaneous vaccinia virus infection, increased expression of the CXCR3 ligands CXCL9 and CXCL10 by skin monocytes was required for effector T cells to locate, engage and kill virus-infected cells[91]. CXCR3-deficient effector T cells in the skin did not penetrate into infected foci and displayed higher migration speed than their wild-type counterparts. However, because CXCR3 has a role in T cell homing to peripheral tissues[92], it remains possible that the fraction of CXCR3-deficient T cells that reach the inflamed skin express a different set of integrins and that this accounts for their altered scanning behaviour. An involvement for chemotaxis in antigen discovery in the inflamed skin has been recently confirmed in a model of herpes simplex virus infection in which the authors, by combining experimental data and simulation, showed a requirement for CXCR3-dependent chemotaxis in T cell–target localization[93]. This is an interesting example that demonstrates the value of combining empirical data and simulation inspired from search theories. Compared with lymph nodes, the frequency of antigen-specific T cells is presumed to be much higher in tissue during the acute phase of an injury as effector T cells are actively recruited, and it is expected that the attraction of effector T cells by APCs to inflamed tissues is an advantageous strategy. Therefore, T cell migration patterns in tissues are dictated by either navigation (that is, informed movement) and/or local reaction (that is, taxis), similar to what has been described for behavioural search patterns (BOX 1).

Migration in the brain. Responses to *Toxoplasma gondii* in the brain lead to a switch in T cell migration patterns from a diffusive random walk to a mixed Lévy walk (REF. 11). *In silico* modelling from imaging data of the infected central nervous system (CNS) provided evidence that an alternation between fast runs and pauses characterizing Lévy walks significantly shortens the time taken by an effector T cell to find an APC in the CNS compared with T cells undergoing a diffusive random walk.

The production of CXCL10 in the infected CNS also served to enhance the ability of effector T cells to control the infection by retaining them in the brain and increasing their overall motility speed without changing the nature of the walk pattern[11]. Interestingly, the brain is, so far, the only tissue in which Lévy walks by T cells have been observed. It is unclear whether Lévy walk patterns occur in other tissues, mainly because the analysis and statistical approaches used are widely different from study to study and, often, migration data are not fitted to any random walk or similar model. However, using similar methodology to that used by Harris *et al.*[11], it was recently shown that T cell migration in lymph nodes was indeed different from the Lévy walk model[29]. It is unclear whether emergent patterns of T cell migration behaviour, such as Lévy walks, are driven by the environmental matrix or represent a specific search strategy. However, one might hypothesize that Lévy walks may be beneficial for T cells to find rare target parasites in the brain, but they are not an efficient strategy in lymph nodes as the long move-length that characterizes Lévy walks would interfere with the intensive DC scanning necessary to find cognate APCs. In the lymph node, a long jump to a new location may not greatly increase the odds of detecting antigens.

Effector T cells have been shown to invade and migrate in both the parenchyma and cortex regions of the brain. In the cortex of the inflamed CNS of mice with experimental autoimmune encephalomyelitis (EAE) or during *T. gondii* infection[94,95], effector T cells migrate on reticular structures of unknown composition. By contrast, the parenchyma supports autoreactive effector T cell migration and their interaction with phagocytic APCs during EAE without providing any obvious structures for guidance[96]. Interestingly, the presence of reticular structures in the cortex correlates with a strong directional migration bias in a model of sterile injury in the context of EAE[97], consistent with haptokinesis or haptotaxis along reticular structures, whereas motility patterns in the parenchyma have been compared to a diffusive random walk[98].

Overall, migration of effector T cells in the CNS is again strongly driven by the environment, which provides both structural guidance and cues that bias T cell migration towards exploitation and restrict exploratory motility.

Migration in tumours. Tumours are unique in comparison to other tissues because they are a site where the effector immune response is suppressed. Here, we propose that tumours provide an example of a site where T cell search strategies are not adapted to the microenvironment, contributing to inefficient reactivation by APCs.

First, the physical tumour microenvironment dictates much of the search patterns, ultimately preventing CTLs from accessing the core of the tumour[99]. This is a major issue for current immunotherapies[100]. CTLs preferentially migrate in regions of loose fibronectin and collagen surrounding the tumour[101], whereas they poorly penetrate dense tumour foci[102]. CD44 expressed on CTLs has been shown to mediate motility in an ectopic model of thymoma[103]. Although the intracellular domain of CD44 is sufficient for intrinsic polarization and basal motility, it is possible that the extracellular domain of CD44 restricts the migration of CTLs on the ECM by binding to hyaluronic acid, thereby limiting CTL access to the core of the tumour. CTL motility is independent of integrins in at least some tumours, as blocking the interactions of β1 and β2 integrins with their ligands did not affect T cell migration in human lung tumour slices[102]. Second, migration information provided by chemokines actively restricts the search patterns of CTLs and may thereby have a key role in protecting the tumour. Stromal cells surrounding pancreatic tumour foci were shown to produce CXCL12, which sequestrated CTLs in the stromal network away from the tumour core[104]. Overall, a reliance on a haptokinetic mode of motility might be the reason for poor access of CTLs to the core of the tumours.

Finally, the high density of innate immune cells recruited during tumorigenesis that can serve as APCs might limit tumour rejection by providing too many ineffective targets for T cell search. Both tumour-associated macrophages (TAMs) and tumour DCs (that is, CD11b$^+$ DCs and CD103$^+$ DCs) can interact with CTLs[99,105], but only CD103$^+$ DCs can efficiently reactivate T cells, leading to tumour immunity[77]. However, CD103$^+$ DCs represents only 1% of the total tumour immune infiltrate[77] and, therefore, TAMs and CD11b$^+$ DCs can be considered as 'obstacles' that engage T cells and reduce the efficiency of effector T cell search to find CD103$^+$ DCs. Like many other aspects of T cell motility, parallels can be found in ecological models, in which high-target density can impair Lévy walks and promote Brownian walks, whenever encounters with targets disrupt previous directionality[106]

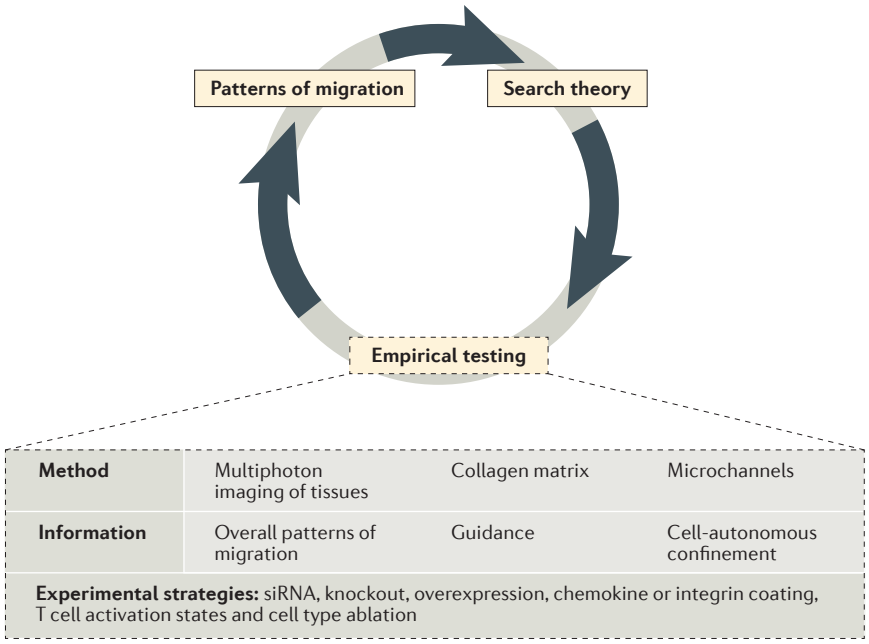


Figure 3 | **Systems biology and integrated studies to unravel 'search' in biology.** The integration of current search theories, empirical testing and the analysis of migration patterns are necessary to understand what governs cell migration and how it relates to search efficiency. Empirical testing can be achieved through a variety of methods, each method unravelling a specific set of information. In immunology (and more broadly in cell biology), migration patterns and validation of search theories can be tested with various experimental strategies, exemplified in the bottom part of the table. siRNA, small interfering RNA.

(BOX 1). This concept is in agreement with the high density of non-effective APCs ($CD11b^+$ DCs and TAMs) and the subdiffusive random migration of CTLs observed in the tumour environment[77,99].

To conclude, T cell search patterns in peripheral tissues are mainly dictated by informed motion (FIG. 1c), in which haptotaxis and haptokinesis cues restrict effector T cell movements, and APCs send chemoattractants to attract effector T cells. Lévy walks have been shown to favour prey detection in the brain, but it is unclear whether Lévy walks are an efficient search strategy in all tissues. Indeed, the frequency of APCs and the presence of haptokinetic and/or chemotactic cues greatly influence the motility patterns of T cells, which range from diffusive to ballistic (FIG. 2).

Conclusion and perspectives

T cell motility and search patterns are intertwined, and it is still unclear which features of T cell motility are important for search efficiency. A comparison of cell motility in different contexts combined with increased information about intrinsic and extrinsic parameters that control search will be the first steps in building cell behavioural search models to decipher whether and how T cell search is optimized. Key areas that remain to be understood include: one, the impact of structural support and other external environments — which ranges from target densities and motility, to spatial distribution and potential obstacles — on search strategies; two, the role of cell-intrinsic factors; and three, the flux of information between the environment and the cell.

Search is a universal requirement, and T cells searching for their cognate antigen follow similar rules and patterns to those of other biological entities. T cell search has been strictly correlated to its pattern of motility, described either as a Brownian walk or as having features of a Lévy walk, mainly by means of fitting data to abstract models without any clear understanding of the causes of such movement patterns nor their relationship to search mechanisms. This is an issue in other fields, such as behavioural ecology[107], but cell biology allows for an integrated comprehension of search patterns by combining fundamental search theory, behaviourally oriented search models and real-time empirical observations (FIG. 3). Another reason the description of Lévy walks has been controversial in the ecology field relates to the fidelity of the various statistical approaches used. How T cell migration statistics are presented and used varies between studies and is probably an important parameter of discrepancy. Effort is currently being made to standardize quantification[108], and this will certainly contribute to a better understanding of the relationship between T cell migration patterns and T cell search.

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1. Blattman, J. N. *et al.* Estimating the precursor frequency of naive antigen-specific CD8 T cells. *J. Exp. Med.* **195**, 657–664 (2002).
2. Jenkins, M. K., Chu, H. H., McLachlan, J. B. & Moon, J. J. On the composition of the preimmune repertoire of T cells specific for peptide-major histocompatibility complex ligands. *Annu. Rev. Immunol.* **28**, 275–294 (2010).
3. Yu, W. *et al.* Clonal deletion prunes but does not eliminate self-specific αβ $CD8^+$ T lymphocytes. *Immunity* **42**, 929–941 (2015).
4. Bajenoff, M. *et al.* Highways, byways and breadcrumbs: directing lymphocyte traffic in the lymph node. *Trends Immunol.* **28**, 346–352 (2007).
5. Fu, H., Wang, A., Mauro, C. & Marelli-Berg, F. T lymphocyte trafficking: molecules and mechanisms. *Front. Biosci. (Landmark Ed.)* **18**, 422–440 (2013).
6. Ley, K. The second touch hypothesis: T cell activation, homing and polarization. *F1000 Res.* **3**, 37 (2014).
7. Hills, T. T., Todd, P. M., Lazer, D., Redish, A. D. & Couzin, I. D. Exploration versus exploitation in space, mind, and society. *Trends Cogn. Sci.* **19**, 46–54 (2015).
8. Codling, E. A., Plank, M. J. & Benhamou, S. Random walk models in biology. *J. R. Soc. Interface* **5**, 813–834 (2008).
9. Miller, M. J., Wei, S. H., Cahalan, M. D. & Parker, I. Autonomous T cell trafficking examined *in vivo* with intravital two-photon microscopy. *Proc. Natl Acad. Sci. USA* **100**, 2604–2609 (2003).
10. Cahalan, M. D. & Parker, I. Choreography of cell motility and interaction dynamics imaged by two-photon microscopy in lymphoid organs. *Annu. Rev. Immunol.* **26**, 585–626 (2008).
11. Harris, T. H. *et al.* Generalized Levy walks and the role of chemokines in migration of effector $CD8^+$ T cells. *Nature* **486**, 545–548 (2012).
12. Worbs, T., Mempel, T. R., Bolter, J., von Andrian, U. H. & Forster, R. CCR7 ligands stimulate the intranodal motility of T lymphocytes *in vivo*. *J. Exp. Med.* **204**, 489–495 (2007).
13. Witt, C. M., Raychaudhuri, S., Schaefer, B., Chakraborty, A. K. & Robey, E. A. Directed migration of positively selected thymocytes visualized in real time. *PLoS Biol.* **3**, e160 (2005).
14. James, A., Plank, M. J. & Brown, R. Optimizing the encounter rate in biological interactions: ballistic versus Levy versus Brownian strategies. *Phys. Rev. E* **78**, 051128 (2008).
15. Krummel, M. F., Sjaastad, M. D., Wulfing, C. & Davis, M. M. Differential clustering of CD4 and CD3ζ during T cell recognition. *Science* **289**, 1349–1352 (2000).
16. Wulfing, C. *et al.* Kinetics and extent of T cell activation as measured with the calcium signal. *J. Exp. Med.* **185**, 1815–1825 (1997).
17. Beauchemin, C., Dixit, N. M. & Perelson, A. S. Characterizing T cell movement within lymph nodes in the absence of antigen. *J. Immunol.* **178**, 5505–5512 (2007).
18. Beltman, J. B., Henrickson, S. E., von Andrian, U. H., de Boer, R. J. & Maree, A. F. Towards estimating the true duration of dendritic cell interactions with T cells. *J. Immunol. Methods* **347**, 54–69 (2009).
19. Preston, S. P., Waters, S. L., Jensen, O. E., Heaton, P. R. & Pritchard, D. I. T-cell motility in the early stages of the immune response modeled as a random walk amongst targets. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **74**, 011910 (2006).
20. Textor, J. *et al.* Defining the quantitative limits of intravital two-photon lymphocyte tracking. *Proc. Natl Acad. Sci. USA* **108**, 12401–12406 (2011).
21. Mrass, P., Petravic, J., Davenport, M. P. & Weninger, W. Cell-autonomous and environmental contributions to the interstitial migration of T cells. *Semin. Immunopathol.* **32**, 257–274 (2010).
22. Miller, M. J., Wei, S. H., Parker, I. & Cahalan, M. D. Two-photon imaging of lymphocyte motility and antigen response in intact lymph node. *Science* **296**, 1869–1873 (2002).
23. Benichou, O., Loverdo, C., Moreau, M. & Voituriez, R. Intermittent search strategies. *Rev. Modern Phys.* **83**, 81–129 (2011).
24. Méndez, V., Campos, D. & Bartumeus, F. *Stochastic Foundations in Movement Ecology* (Springer, 2014).
25. Beltman, J. B., Maree, A. F., Lynch, J. N., Miller, M. J. & de Boer, R. J. Lymph node topology dictates T cell migration behavior. *J. Exp. Med.* **204**, 771–780 (2007).
26. Woolf, E. *et al.* Lymph node chemokines promote sustained T lymphocyte motility without triggering stable integrin adhesiveness in the absence of shear forces. *Nat. Immunol.* **8**, 1076–1085 (2007).
27. Lammermann, T. *et al.* Rapid leukocyte migration by integrin-independent flowing and squeezing. *Nature* **453**, 51–55 (2008).
28. Katakai, T., Habiro, K. & Kinashi, T. Dendritic cells regulate high-speed interstitial T cell migration in the lymph node via LFA-1/ICAM-1. *J. Immunol.* **191**, 1188–1199 (2013).
29. Banigan, E. J., Harris, T. H., Christian, D. A., Hunter, C. A. & Liu, A. J. Heterogeneous $CD8^+$ T cell migration in the lymph node in the absence of inflammation revealed by quantitative migration analysis. *PLoS Comput. Biol.* **11**, e1004058 (2015).
30. Bajenoff, M. *et al.* Stromal cell networks regulate lymphocyte entry, migration, and territoriality in lymph nodes. *Immunity* **25**, 989–1001 (2006).
31. Katakai, T., Hara, T., Sugai, M., Gonda, H. & Shimizu, A. Lymph node fibroblastic reticular cells construct the stromal reticulum via contact with lymphocytes. *J. Exp. Med.* **200**, 783–795 (2004).
32. Mempel, T. R., Junt, T. & von Andrian, U. H. Rulers over randomness: stroma cells guide lymphocyte migration in lymph nodes. *Immunity* **25**, 867–869 (2006).
33. Malhotra, D. *et al.* Transcriptional profiling of stroma from inflamed and resting lymph nodes defines immunological hallmarks. *Nat. Immunol.* **13**, 499–510 (2012).
34. Luther, S. A., Tang, H. L., Hyman, P. L., Farr, A. G. & Cyster, J. G. Coexpression of the chemokines ELC and SLC by T zone stromal cells and deletion of the ELC gene in the plt/plt mouse. *Proc. Natl Acad. Sci. USA* **97**, 12694–12699 (2000).
35. Asperti-Boursin, F., Real, E., Bismuth, G., Trautmann, A. & Donnadieu, E. CCR7 ligands control basal T cell motility within lymph node slices in a phosphoinositide 3-kinase-independent manner. *J. Exp. Med.* **204**, 1167–1179 (2007).
36. Katakai, T., Kondo, N., Ueda, Y. & Kinashi, T. Autotaxin produced by stromal cells promotes LFA-1-independent and Rho-dependent interstitial T cell motility in the lymph node paracortex. *J. Immunol.* **193**, 617–626 (2014).
37. Graw, F. & Regoes, R. R. Influence of the fibroblastic reticular network on cell-cell interactions in lymphoid organs. *PLoS Comput. Biol.* **8**, e1002436 (2012).
38. Gerard, A. *et al.* Detection of rare antigen-presenting cells through T cell-intrinsic meandering motility, mediated by Myo1g. *Cell* **158**, 492–505 (2014).
39. Bartumeus, F., Raposo, E. P., Viswanathan, G. M. & da Luz, M. G. Stochastic optimal foraging: tuning intensive and extensive dynamics in random searches. *PLoS ONE* **9**, e106373 (2014).
40. Mandl, J. N. *et al.* Quantification of lymph node transit times reveals differences in antigen surveillance strategies of naive $CD4^+$ and $CD8^+$ T cells. *Proc. Natl Acad. Sci. USA* **109**, 18036–18041 (2012).
41. Friedl, P. & Gunzer, M. Interaction of T cells with APCs: the serial encounter model. *Trends Immunol.* **22**, 187–191 (2001).

42. Gunzer, M. *et al.* Antigen presentation in extracellular matrix: interactions of T cells with dendritic cells are dynamic, short lived, and sequential. *Immunity* **13**, 323–332 (2000).
43. Moreau, H. D. *et al.* Signal strength regulates antigen-mediated T-cell deceleration by distinct mechanisms to promote local exploration or arrest. *Proc. Natl Acad. Sci. USA* **112**, 12151–12156 (2015).
44. Joshi, N. S. *et al.* Inflammation directs memory precursor and short-lived effector CD8$^+$ T cell fates via the graded expression of T-bet transcription factor. *Immunity* **27**, 281–295 (2007).
45. Badovinac, V. P., Messingham, K. A., Jabbari, A., Haring, J. S. & Harty, J. T. Accelerated CD8$^+$ T-cell memory and prime-boost response after dendritic-cell vaccination. *Nat. Med.* **11**, 748–756 (2005).
46. Kaech, S. M. & Wherry, E. J. Heterogeneity and cell-fate decisions in effector and memory CD8$^+$ T cell differentiation during viral infection. *Immunity* **27**, 393–405 (2007).
47. Gerner, M. Y., Torabi-Parizi, P. & Germain, R. N. Strategically localized dendritic cells promote rapid T cell responses to lymph-borne particulate antigens. *Immunity* **42**, 172–185 (2015).
48. Woodruff, M. C. *et al.* Trans-nodal migration of resident dendritic cells into medullary interfollicular regions initiates immunity to influenza vaccine. *J. Exp. Med.* **211**, 1611–1621 (2014).
49. Gerard, A. *et al.* Secondary T cell-T cell synaptic interactions drive the differentiation of protective CD8$^+$ T cells. *Nat. Immunol.* **14**, 356–363 (2013).
50. Sabatos, C. A. *et al.* A synaptic basis for paracrine interleukin-2 signaling during homotypic T cell interaction. *Immunity* **29**, 238–248 (2008).
51. Ferguson, A. R. & Engelhard, V. H. CD8 T cells activated in distinct lymphoid organs differentially express adhesion proteins and coexpress multiple chemokine receptors. *J. Immunol.* **184**, 4079–4086 (2010).
52. Sallusto, F. *et al.* Switch in chemokine receptor expression upon TCR stimulation reveals novel homing potential for recently activated T cells. *Eur. J. Immunol.* **29**, 2037–2045 (1999).
53. Mueller, S. N. *et al.* Regulation of homeostatic chemokine expression and cell trafficking during immune responses. *Science* **317**, 670–674 (2007).
54. Castellino, F. *et al.* Chemokines enhance immunity by guiding naive CD8$^+$ T cells to sites of CD4$^+$ T cell-dendritic cell interaction. *Nature* **440**, 890–895 (2006).
55. Hugues, S. *et al.* Dynamic imaging of chemokine-dependent CD8$^+$ T cell help for CD8$^+$ T cell responses. *Nat. Immunol.* **8**, 921–930 (2007).
56. Hickman, H. D. *et al.* Chemokines control naive CD8$^+$ T cell selection of optimal lymph node antigen presenting cells. *J. Exp. Med.* **208**, 2511–2524 (2011).
57. Eickhoff, S. *et al.* Robust anti-viral immunity requires multiple distinct T cell-dendritic cell interactions. *Cell* **162**, 1322–1337 (2015).
58. Hor, J. L. *et al.* Spatiotemporally distinct interactions with dendritic cell subsets facilitates CD4 and CD8 T cell activation to localized viral infection. *Immunity* **43**, 554–565 (2015).
59. Kelner, G. S. *et al.* Lymphotactin: a cytokine that represents a new class of chemokine. *Science* **266**, 1395–1399 (1994).
60. Dorner, B. G. *et al.* Selective expression of the chemokine receptor XCR1 on cross-presenting dendritic cells determines cooperation with CD8$^+$ T cells. *Immunity* **31**, 823–833 (2009).
61. Lei, Y. & Takahama, Y. XCL1 and XCR1 in the immune system. *Microbes Infect.* **14**, 262–267 (2012).
62. Groom, J. R. *et al.* CXCR3 chemokine receptor-ligand interactions in the lymph node optimize CD4$^+$ T helper 1 cell differentiation. *Immunity* **37**, 1091–1103 (2012).
63. Hu, J. K., Kagari, T., Clingan, J. M. & Matloubian, M. Expression of chemokine receptor CXCR3 on T cells affects the balance between effector and memory CD8 T-cell generation. *Proc. Natl Acad. Sci. USA* **108**, E118–E127 (2011).
64. Kurachi, M. *et al.* Chemokine receptor CXCR3 facilitates CD8$^+$ T cell differentiation into short-lived effector cells leading to memory degeneration. *J. Exp. Med.* **208**, 1605–1620 (2011).
65. Campbell, D. J., Kim, C. H. & Butcher, E. C. Separable effector T cell populations specialized for B cell help or tissue inflammation. *Nat. Immunol.* **2**, 876–881 (2001).
66. Reif, K. *et al.* Balanced responsiveness to chemoattractants from adjacent zones determines B-cell position. *Nature* **416**, 94–99 (2002).
67. Okada, T. *et al.* Antigen-engaged B cells undergo chemotaxis toward the T zone and form motile conjugates with helper T cells. *PLoS Biol.* **3**, e150 (2005).
68. Mempel, T. R., Henrickson, S. E. & Von Andrian, U. H. T-cell priming by dendritic cells in lymph nodes occurs in three distinct phases. *Nature* **427**, 154–159 (2004).
69. Tan, J. T. & Surh, C. D. T cell memory. *Curr. Top. Microbiol. Immunol.* **311**, 85–115 (2006).
70. Kastenmuller, W. *et al.* Peripheral prepositioning and local CXCL9 chemokine- mediated guidance orchestrate rapid memory CD8$^+$ T cell responses in the lymph node. *Immunity* **38**, 502–513 (2013).
71. Sung, J. H. *et al.* Chemokine guidance of central memory T cells is critical for antiviral recall responses in lymph nodes. *Cell* **150**, 1249–1263 (2012).
72. Vergassola, M., Villermaux, E. & Shraiman, B. I. 'Infotaxis' as a strategy for searching without gradients. *Nature* **445**, 406–409 (2007).
73. Griffith, J. W., Sokol, C. L. & Luster, A. D. Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu. Rev. Immunol.* **32**, 659–702 (2014).
74. Marelli-Berg, F. M., Cannella, L., Dazzi, F. & Mirenda, V. The highway code of T cell trafficking. *J. Pathol.* **214**, 179–189 (2008).
75. Bromley, S. K., Mempel, T. R. & Luster, A. D. Orchestrating the orchestrators: chemokines in control of T cell traffic. *Nat. Immunol.* **9**, 970–980 (2008).
76. Guo, L. *et al.* Innate immunological function of T_H2 cells *in vivo*. *Nat. Immunol.* **16**, 1051–1059 (2015).
77. Broz, M. L. *et al.* Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell* **26**, 638–652 (2014).
78. Chang, T. T., Jabs, C., Sobel, R. A., Kuchroo, V. K. & Sharpe, A. H. Studies in B7-deficient mice reveal a critical role for B7 costimulation in both induction and effector phases of experimental autoimmune encephalomyelitis. *J. Exp. Med.* **190**, 733–740 (1999).
79. Krummel, M. F., Heath, W. R. & Allison, J. Differential coupling of second signals for cytotoxicity and proliferation in CD8$^+$ T cell effectors: amplification of the lytic potential by B7. *J. Immunol.* **163**, 2999–3006 (1999).
80. Lindsay, R. S. *et al.* Antigen recognition in the islets changes with progression of autoimmune islet infiltration. *J. Immunol.* **194**, 522–530 (2015).
81. Friedman, R. S. *et al.* An evolving autoimmune microenvironment regulates the quality of effector T cell restimulation and function. *Proc. Natl Acad. Sci. USA* **111**, 9223–9228 (2014).
82. Thornton, E. E. *et al.* Spatiotemporally separated antigen uptake by alveolar dendritic cells and airway presentation to T cells in the lung. *J. Exp. Med.* **209**, 1183–1199 (2012).
83. Overstreet, M. G. *et al.* Inflammation-induced interstitial migration of effector CD4$^+$ T cells is dependent on integrin αV. *Nat. Immunol.* **14**, 949–958 (2013).
84. Honda, T. *et al.* Tuning of antigen sensitivity by T cell receptor-dependent negative feedback controls T cell effector function in inflamed tissues. *Immunity* **40**, 235–247 (2014).
85. Sorokin, L. The impact of the extracellular matrix on inflammation. *Nat. Rev. Immunol.* **10**, 712–723 (2010).
86. DiMilla, P. A., Barbee, K. & Lauffenburger, D. A. Mathematical model for the effects of adhesion and mechanics on cell migration speed. *Biophys. J.* **60**, 15–37 (1991).
87. Baron, J. L., Reich, E. P., Visintin, I. & Janeway, C. A. Jr. The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between α4- integrins and vascular cell adhesion molecule-1. *J. Clin. Invest.* **93**, 1700–1708 (1994).
88. Ray, S. J. *et al.* The collagen binding α1β1 integrin VLA-1 regulates CD8 T cell-mediated immune protection against heterologous influenza infection. *Immunity* **20**, 167–179 (2004).
89. Richter, M. *et al.* Collagen distribution and expression of collagen-binding α1β1 (VLA-1) and α2β1 (VLA-2) integrins on CD4 and CD8 T cells during influenza infection. *J. Immunol.* **178**, 4506–4516 (2007).
90. Natsuaki, Y. *et al.* Perivascular leukocyte clusters are essential for efficient activation of effector T cells in the skin. *Nat. Immunol.* **15**, 1064–1069 (2014).
91. Hickman, H. D. *et al.* CXCR3 chemokine receptor enables local CD8$^+$ T cell migration for the destruction of virus-infected cells. *Immunity* **42**, 524–537 (2015).
92. Groom, J. R. & Luster, A. D. CXCR3 in T cell function. *Exp. Cell Res.* **317**, 620–631 (2011).
93. Ariotti, S. *et al.* Subtle CXCR3-dependent chemotaxis of CTLs within infected tissue allows efficient target localization. *J. Immunol.* **195**, 5285–5295 (2015).
94. Wilson, E. H. *et al.* Behavior of parasite-specific effector CD8$^+$ T cells in the brain and visualization of a kinesis-associated system of reticular fibers. *Immunity* **30**, 300–311 (2009).
95. Herz, J. *et al.* *In vivo* imaging of lymphocytes in the CNS reveals different behaviour of naive T cells in health and autoimmunity. *J. Neuroinflamm.* **8**, 131 (2011).
96. Bartholomaus, I. *et al.* Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. *Nature* **462**, 94–98 (2009).
97. Kim, J. V. *et al.* Two-photon laser scanning microscopy imaging of intact spinal cord and cerebral cortex reveals requirement for CXCR6 and neuroinflammation in immune cell infiltration of cortical injury sites. *J. Immunol. Methods* **352**, 89–100 (2010).
98. Kawakami, N. *et al.* Live imaging of effector cell trafficking and autoantigen recognition within the unfolding autoimmune encephalomyelitis lesion. *J. Exp. Med.* **201**, 1805–1814 (2005).
99. Engelhardt, J. J. *et al.* Marginating dendritic cells of the tumor microenvironment cross-present tumor antigens and stably engage tumor-specific T cells. *Cancer Cell* **21**, 402–417 (2012).
100. Joyce, J. A. & Fearon, D. T. T cell exclusion, immune privilege, and the tumor microenvironment. *Science* **348**, 74–80 (2015).
101. Mrass, P. *et al.* Random migration precedes stable target cell interactions of tumor-infiltrating T cells. *J. Exp. Med.* **203**, 2749–2761 (2006).
102. Salmon, H. *et al.* Matrix architecture defines the preferential localization and migration of T cells into the stroma of human lung tumors. *J. Clin. Invest.* **122**, 899–910 (2012).
103. Mrass, P. *et al.* CD44 mediates successful interstitial navigation by killer T cells and enables efficient antitumor immunity. *Immunity* **29**, 971–985 (2008).
104. Feig, C. *et al.* Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc. Natl Acad. Sci. USA* **110**, 20212–20217 (2013).
105. Boissonnas, A. *et al.* CD8$^+$ tumor-infiltrating T cells are trapped in the tumor-dendritic cell network. *Neoplasia* **15**, 85–94 (2013).
106. de Jager, M. *et al.* How superdiffusion gets arrested: ecological encounters explain shift from Levy to Brownian movement. *Proc. R. Soc. B* **281**, 20132605 (2013).
107. Bartumeus, F. Behavioural ecology cannot turn its back on Levy walk research: comment on "Liberating Levy walk research from the shackles of optimal foraging" by A. M. Reynolds. *Phys. Life Rev.* **14**, 84–86 (2015).
108. Letendre, K., Donnadieu, E., Moses, M. E. & Cannon, J. L. Bringing statistics up to speed with data in analysis of lymphocyte motility. *PLoS ONE* **10**, e0126333 (2015).
109. Dusenbery, D. B. *Sensory ecology: how organisms acquire and respond to information.* (W. H. Freeman, 1992).
110. Mischiati, M. *et al.* Internal models direct dragonfly interception steering. *Nature* **517**, 333–338 (2015).
111. Lima, S. L. & Zollner, P. A. Towards a behavioral ecology of ecological landscapes. *Trends Ecol. Evol.* **11**, 131–135 (1996).
112. Nathan, R. *et al.* A movement ecology paradigm for unifying organismal movement research. *Proc. Natl Acad. Sci. USA* **105**, 19052–19059 (2008).
113. Campos, D., Bartumeus, F. & Mendez, V. Search times with arbitrary detection constraints. *Phys. Rev. E* **88**, 022101 (2013).
114. Viswanathan, G. M., da Luz, M. G. E., Raposo, E. P. & Stanley, H. E. *The Physics of Foraging* (Cambridge Univ. Press, 2011).
115. Dieterich, P., Klages, R., Preuss, R. & Schwab, A. Anomalous dynamics of cell migration. *Proc. Natl Acad. Sci. USA* **105**, 459–463 (2008).

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Competing interests statement
The authors declare no competing interests.