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T-cell Migration, Search Strategies and Mechanisms

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Abstract

T cell migration is essential for T cell responses, allowing for detection of cognate antigen at the surface of an Antigen-Presenting Cell (APC) and for interactions with other cells involved in the immune response. Although appearing random, growing evidence supports that T cell motility patterns are strategic and governed by mechanisms that are optimized for both activation-stage and environment-specific attributes. In this Opinion Article, we will discuss how to understand the combined effects of T cell- intrinsic and -extrinsic forces upon these motility patterns when viewed in highly complex tissues filled with other cells involved in parallel motility. In particular, we will examine how insights from 'search theory' describe T cell movement across exploitation-exploration gradients, in the context of activation versus effector function and in the context of lymph nodes versus peripheral tissues.

Introduction

Every T cell expresses a specific T Cell Receptor (TCR), which is able to recognize a limited variety of peptides bound to major histocompatibility complexes (pMHC) at the surface of an APC. As a consequence, about one T cell in 10^5-10^6 is specific for a given antigen, referred to as its cognate antigen[1-3]. During an immune response, a T cell will have to encounter its cognate antigen multiple times in different contexts and tissues.

The varying requirements for T cells to move and recognize APCs and targets can be best appreciated across the lifetime of the immune response, as it shifts from lymphoid organs to target organs. The initial encounter between naïve T cells and their cognate antigen in the context of an APC usually happens in secondary lymphoid organs, including Lymph Nodes (LNs) (Figure 1A). LNs are highly organized, providing a confined and structured architecture facilitating T cell scanning of potential APCs, especially Dendritic cells (DCs) coming from different tissues[4]. Prior to the introduction of a putative antigen leading to TCR recognition, all naive T cells are generic; naïve T cells lack information to differentiate DCs that are antigen-specific from non-specific. Recently activated T cells, in contrast, upregulate mechanisms and receptors that modify their migration patterns and link them to other cells that have been triggered; these additional mechanisms allow them to find and reside within an inflammatory microenvironment to undergo and induce proper differentiation (Figure 1B). Most differentiated effector T cells then leave LNs to access and scan peripheral tissues

to once again find their antigen[5] (Figure 1C): this antigen reencounter results in killing of infected host cells by effector T cells and maintenance of T cell effector functions[6].

The principal purpose of T cell motility is to 'search' for APCs, signaling partners or targets. The process of search is a fundamental requirement in almost any biological systems where multiple agents (i.e. cells, organisms) reside within an ecosystem much larger than their perceptual capabilities. T cells fit this criterion and this article will build upon search theories originating from other fields, including ecology, to describe T cell behavior across different tissues.

Because the immune response must detect and respond to antigen stimulation quickly to eradicate pathogens or tumor 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 TCRs and pMHC to engage and induce their activation. Motility undertaken by T cells should likely resolve, in different contexts and by different mechanisms, the classic exploitation-exploration tradeoff[7] (Box 1). In essence, to be most efficient, T cells balance motility strategies that exploit available information (sensing integrins, chemokines and pMHC; providing 'expectations' to determine where to move) and exploring for new information (sampling the environment, typically without as much sensory instruction).

As with many biological movements[8], T cell motility was initially characterized as resembling a random walk[9]; this being defined by stochastic movements with trajectories that consists 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 found[12] (Box 1). Beyond these, T cells can under some circumstances and for short times undergo fully ballistic migration (i.e. in a nearly straight line)[13] (Figure 2).

This spectrum of motility (Figure 2) is generated by combination of: cell-intrinsic locomotion (e.g. rates of actin polymerization, location of cortex contraction), physical guidance from the microenvironment (e.g. collagen fiber or stromal cells orientation), and chemical information provided by the environment (e.g. chemokines, antigen dose and costimulation).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, with consequences for the global search efficiency. In this article, we will explore how coordination between the properties of the tissue microenvironment, the information provided by other cells such as other T cells and APCs and cell-intrinsic motility behavior of T cells may optimize search processes and therefore immune responses.

1- T cell search in LNs

One of the most efficient strategies to find a prey in a simplistic system is to detect the prey location and move ballistically towards it[14]. This behavior is not typically observed during naïve T cell search in LNs. An intuitive reason for this is that T cells cannot know that their antigen is being presented by a given APC in order to move toward it. Because the fraction of naïve T cells specific for any antigen is extremely small[1], the best strategy is to provide a relatively equal chance for all clones to scan a given APC. Directional movement toward an incoming APC might create a bottleneck caused by the multitude of T cell clones with poor specificity for peptides on this APC that would be attracted. We will therefore argue that T cell search in LNs is initially information-poor and exploration-based mechanisms are favored. Additionally physical barriers to access APCs introduced by endothelium, stroma or other cells may also be responsible for apparent random migration.

A final consideration for motility strategy is the latency of detection upon encounter. While T cells are apparently sensitive to single pMHC complexes when those are presented in a dish, even in those contexts T cell typically have to stay in contact with their APC at least a minute in order to get primed[15, 16]. Therefore, motility strategies are not necessarily efficient per se, but are adapted to the complexity of the system; in this case to the combined need to touch an APC and then dwell long enough to signal.

Naïve T cells: non-informed motion—Within the T cell zone of LNs, T cells display features of a diffusive (Brownian-type) or subdiffusive random walk[9, 17-20] (Figure 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 LNs could be the consequence of the heterogeneity of the microenvironment or the presence of obstacles[25]. Empirical evidence suggests that speed fluctuations are partially linked to integrins; T cells[26] and other immune cells[27] do not require integrins to efficiently move in LNs, but the bursts of high speed observed during T cell motility are mediated by LFA-1 on T cells interacting with ICAM-1 expressed on DCs[28]. Alternatively, it has recently been shown that fluctuation could be linked to heterogeneous T cell movements, described by a two-population model of persistent and diffusive random walkers[29].

It has also been proposed that random walk of naïve T cells is supported by a network of fibroblast reticular cells (FRCs)[30, 31], leading to the description of “guided random walk”[32]. FRCs express chemoattractants CCL19, CCL21, and CXCL12[33, 34], which are required for optimal naïve T cell motility *in vivo*[26, 31, 33, 35], consistent with a model of **chemokinesis**. LPA, another chemoattractant produced by stromal cells, has also recently been implicated in T cell motility in LNs, as interstitial T cell migration is reduced when LPA production by autotaxin is inhibited[36]. In some areas of the LN, the space between FRC fibers is large enough to accommodate multiple T cells, suggesting that some T cells do not contact FRC fibers. Thus, while some cells may be ‘guided’ by these FRCs, others likely push off of one another to migrate.

Cues from the environment seem to have minimal impact on the directionality of migration. Chemokines present in the LN increase basal T cell motility (**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, while the receptor for CCL19/21, CCR7, is required on T cells for maintaining their average speed, it does not control all 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 finding rare APCs[37].

Speed fluctuations 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, contributes 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* modeling and empirical data show that, although Myo1g deficient cells cover territory more quickly, 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 and adhesion to integrins, this suggests that speed fluctuations and turning patterns are intrinsically tuned to adjust the fundamental speed-perception and intensive-extensive search tradeoffs, as it was similarly defined in some behavioral studies[24, 39].

In effect, the above study demonstrates that T cells are intrinsically tuned for search. One key question is how Myo1g activity may be regulated, transcriptionally or at the protein level, so as to tune ballistic versus intensive search. Also, as we move beyond this finding, it is generally important to consider how cells tune their intrinsic motility based on their function. For example, DC scanning dynamics within LNs are different between CD4 and 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 appears to take advantage of multiple ‘preys’ and T cells frequently engage in motile synaptic interactions with different APCs. This may permit them to hone in on the ‘best’ APC or to convert to a ‘swarm’ as discussed below. Serial T cell - APC encounter[41] also allows T cells to collect a series of short signals by different APCs until a critical activation threshold is achieved[42]. This might especially be relevant for T cells that have a low affinity for their cognate peptide. Whereas high affinity cognate peptide induces arrest and stable T-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 favor local exploitation so as to accumulate more TCR signaling.

Recently Activated T cells: Increased Expectation and Informed motion—Once naïve T cells find their cognate antigen and a T cell immune response is initiated, activated T cells have to find and reside within the inflammatory microenvironment that is required for their proper differentiation into effector or memory T cell subsets. The exact composition of

the effector environment is not fully understood but it is well established that CD8 T cells require combinations of inflammatory signals[44, 45], APC licensing and CD4 T cell help for their differentiation[46]. It has been recently observed that APCs themselves undergo migration, and ultimately aggregate in the interfollicular region (IFR) of LNs together with recently activated CD4 and CD8 T cells[47-50], suggesting that APCs might guide T cell relocation to a “differentiating” microenvironment[48]. It has also been shown that activated T cells up-regulate a variety of chemokine receptors[51, 52] and thereby acquire sensitivity for additional chemoattractant cues. Concomitantly, FRCs gradually down-regulate homeostatic chemokines CCL19/21 after the initiation of the immune response[33, 53]. As a result, T cell motility patterns shift from random toward environmentally guided migration (i.e. they have increased ‘expectation’; Box 1 and Figure 1B).

One of the first pieces of evidence that T cell are ‘guided’ to a differentiating environment by APCs was provided by the discovery that APCs interacting with CD4 helper T cells produce CCL3/4[54]. Recently activated, but not naïve, CD8 T cells up-regulate CCR5[54, 55], enabling them to respond to CCL3/4, likely produced by APCs[56], and get CD4 help[54]. DCs expressing the chemokine receptor XCR1 have similarly been recently described as the DC subset bringing CD4 and CD8 T cells into close proximity in the context of viral infections[57, 58]. Interestingly, T cells secrete the XCR1 ligand XCL1 soon after activation[59]. XCL1 has been shown to attract DCs *in vitro* and regulate T cell effector function[60, 61]. Although the control of DC and T cell migration by the XCR1/XCL1 axis remains to be established, it is tempting to speculate that XCL1 reinforces T/APC comigration and coalescence.

CXCL9 is also attracts recently activated T cells, particularly in the spleen where it favors CD8 T cell commitment to terminal effectors[62, 63]. Expression of CXCL9 receptor, CXCR3, on activated CD8 T cells preferentially promotes 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 favors T cell commitment to effector as opposed to memory cells.

Finally, shifted chemokine balance following the initiation of the immune response has also been shown to contribute to T cell encounter with B cells with the goal to help B cells differentiate without disrupting the overall LN 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 CXCR5 ligand CXCL13 is expressed[65]. Concomitantly, activated B cells undergo transiently increase CCR7[66]. This coordinated response results in efficient T–B-cell encounters at the edge of follicles where B cells receive CD4 cell help.

Overall, current data support the model that recently activated T cells shift towards ‘exploitative’ motility patterns driven by **chemotaxis,** allowing them to sense information coded by other members of 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 T-B border where activated B cells and T cells both migrate toward one another[67].

Concomitant searches, followed by each individual cell generating an information-rich environment ripe for exploitation behavior, is likely the source of ‘swarms’ of early-activated T cells around APCs that are observed in LNs after initial recognition[68]. These are likely important for sharing cytokines and tuning effector differentiation in addition to providing a niche for proliferation. As we study swarms in future, it may be useful to think of them as ‘linked’ searches, in which each cells 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, which have features that allow more rapid responses upon exposure to recall antigen as compared to naïve T cells[69]. In LNs, memory CD8 T cells do not reside in the deep paracortex like naïve T cells but are mostly found beneath B cell follicles close to high endothelial venules, strategically prepositioned to rapidly encounter cells infected by pathogens spread via lymphatics[70]. Furthermore, after viral infection, memory T cells are more efficient at detecting and responding to viral antigen within the first few hours in peripheral areas of LNs, which are poorly accessible to naïve T cells[71]. Accelerated detection of antigen by memory T cells is directed by a coordinated cascade of cytokines and chemokines. Memory T cells residing at the LN periphery undergo rapid arrest on the infected cells and secrete IFN-γ that induces CXCL9 expression from local myeloid and stromal cells. CXCL9 acts in as a feed-forward loop to amplify the response by recruiting more CXCR3+ memory CD8 T cells to the infected region[70, 71].

Ecological behavior studies show that animal search is influenced by the quality and nature of prior encounter/information given by the environment[72]. For memory T cells, prior encounter results in their prepositioning at sites where infection is likely to first appear and allows for rapid recruitment upon secondary infection. Different T cell subsets 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.

2- Effector T cell search in peripheral tissues

After differentiation, T cells acquire the capacity to produce effector cytokines and leave the LNs. Through the expression of specific tissue-homing receptors, these then access peripheral tissues, with the goal of eliminating invading pathogens or tumor cells. The mechanisms controlling effector T cell recruitment to tissues has been extensively reviewed elsewhere[73-75], and will not be addressed here but would clearly correspond to a cue-guided motility event (Figure 1C).

After effector T cells enter an inflamed peripheral tissue, effector functions are prompted by either antigen-dependent or independent stimuli (e.g, cytokines[76]). In the case of antigen-driven reactivation, effector T cells have to once again find their cognate peptide. For example, reactivation happens in the context of a mouse model of breast cancer, where CD103+ DCs are found in close proximity to effector CD8 T cells, or cytotoxic T Lymphocytes (CTLs), at the tumor site and can reactivate antigen-specific T cells[77]. In this context, CTLs must locate APCs to maintain cytotoxicity[78, 79]. Similarly, CTLs interact with DCs in the pancreas during Type 1 Diabetes[80], necessary for optimal effector function and disease progression[81]. CD4 T cells similarly reencounter antigen in tissues. In the lung of

mice with allergic inflammation, CD4 T cells form conjugates with lung-resident DCs, resulting in TCR signaling[82]. Finally, antigen-specific CD4 T cells present in the skin during Contact Hypersensitivity (CHS) exhibited reduced velocity and high IFN-γ production immediately after TCR engagement[83, 84], consistent with a role of antigen reencounter in maintaining effector functions.

Stimulation of effector T cell in peripheral tissues has different requirements than naïve T cell priming in LNs and this likely further alters the exploitation-exploration tradeoff. First, the frequency of T/APC encounter in the inflamed tissue is presumed to be much higher than to the one found in LNs, as most T cells recruited to the inflamed site will be antigen specific. Second, costimulation is not strictly necessary for effector T cell stimulation[79] as opposed to naïve T cells.

Migration in the skin—Most peripheral tissues are characterized by a dense ECM (Extra-Cellular Matrix) network and changes in it results in changes in search in the skin. Inflammatory mediators, in particular TGFβ, TNFα and IFNγ affect protease secretion and ECM turnover[85]. In a mouse model of Complete Freund Adjuvant (CFA)-induced dermal inflammation, the ECM network loosens[83]. In contrast to LNs where integrin adherence is dispensable, this loose network results in integrin αv-dependent T cell migration[83]. This type of motility, **haptokinesis,** is common in mesenchymal cells[86]. The same type of migration likely takes place in the diabetic pancreas and in the lung during influenza infection, as infiltrating T cells express high level of collagen-binding integrins[83, 87-89].

The local environment in the inflamed skin also aggregates the antigen in a common location, leading to enhanced efficiency of search if T cells can follow chemotactic cues to these depots. Indeed, a recent study has shown that during CHS (Contact Hyper Sensitivity), CXCL2 production by macrophages attracts dermal APCs, forming clusters[90]. Effector T cells have to these clusters proliferate and produce cytokines[90]. Whether APCs actively attract effector T cells in this context is unclear but similar movements and aggregations of DC are also observed in LNs where they likely 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. In a mouse model of epicutaneous vaccinia virus infection, increased expression of the CXCR3 ligands CXCL9/10 expressed 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 speed than their wild-type counterparts. However, because CXCR3 is required for homing to peripheral tissues[92], it remains possible that the fraction of CXCR3 deficient T cells reaching the skin express a different set of integrins and that this accounts for their altered scanning behavior. The involvement of chemotaxis has been recently confirmed in a model of HSV infection, where the authors, by combining experimental data and simulation, unraveled the requirement of subtle CXCR3-dependent chemotaxis for target localization[93]. This is an interesting example demonstrating the value of combining empirical data and simulation inspired from search theories. Compared to LNs, the frequency of antigen-specific T cells will be much higher in tissue during the acute phase of

an injury, as effector T cells are actively recruited. Whereas not favorable in LNs, it is expected that attraction of effector T cells by APCs in tissues is an advantageous strategy. This results in migration patterns that are dictated by either navigation (informed movement) and/or local reaction (taxis), as described for behavioral patterns.

Migration in the brain—Responses to Toxoplasm gondi in the brain leads to a switch from diffusive random patterns to mixed 'Lévy walk'[11]. *In silico* modeling from imaging data acquired in the CNS provided evidence that alternation of fast runs and pauses significantly shortens the time taken to find an APC in the CNS compared to a diffusive random walk. CXCL10 in this setting 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 where Lévy walks have been observed. It is unclear whether Lévy walk patterns can be found in other tissues, mainly because analysis and statistical approaches are widely different from study to study, and data is often not fitted to any consistent model. However, using similar methodology as in Harris et al[11], it was recently shown that migration in LNs was indeed significantly different from the generalized Lévy walk model[29]. It is unclear whether emergent patterns like Lévy walks are driven by the environmental matrix or represent search. However, one might hypothesize that Lévy walks may be beneficial for T cells to find rare target parasites in the brain, but not an efficient strategy in LNs as the long move-length that characterizes Lévy walks would interfere with the intensive DC scanning necessary to find cognate APCs. In the LN, a long jump to a new location may not significantly increase the odds of detecting antigens.

Effector T cells have been shown to invade and migrate in both the parenchyma and cortex. In the cortex of the inflamed CNS of mice with Experimental Autoimmune Encephalomyelitis (EAE) or during Toxoplasma gondii infection[94, 95], effector T cells migrate on reticular structures of unknown composition. The parenchyma, however, supports effector auto-reactive T cells migration and interaction with phagocytic APCs during EAE without providing any obvious structures for guidance[96]. Interestingly, the presence of reticular structures in the cortex results in a strong directional migration bias in a model of sterile injury in the context of EAE[97], whereas motility patterns in the parenchyma have been compared to a diffusive random walk[98].

Overall, migration of effector cells in the CNS is again strongly driven by the environment, which provides both structural guidance and cues biasing towards exploitation and restricting exploratory motility.

Migration in tumors—Tumors are unique in comparison to other tissues because it is a site where the effector response is thwarted. In this paragraph, we will argue that tumors provide an example for which search strategies are being disrupted, contributing to inefficient reactivation by APC.

First, the physical environment of a tumor dictates much of the search patterns, ultimately preventing the ability of CTLs to access the core of the tumor[99], which constitutes a major issue for current immunotherapies[100]. CTLs preferentially migrate in regions of loose

fibronectin and collagen surrounding the tumor[101], whereas they poorly penetrate dense tumor foci[102]. CD44 expressed on CTLs mediates motility in an ectopic model of thymoma[103]. In this context, whereas the intracellular domain of CD44 is required for intrinsic polarization and basal motility, it is possible that the extracellular domain of CD44 restricts migration to ECM through HA binding. Motility is independent of integrins in at least some tumors, as blocking the interactions of β1 and β2 integrins with their ligands does not affect T cell migration in human lung tumor slices[102].

In addition, information in the form of chemokines actively restricts the search patterns and may thereby play a key role in protecting the tumor. Stromal cells surrounding pancreatic tumor foci produce CXCL12, sequestrating CTLs in the stromal network away from the tumor core[104]. Overall, reliance on a haptokinetic mode of motility might be the reason for poor access to the core of the tumors.

Finally, the high density of immune cells recruited during carcinogenesis might surprisingly limit tumor rejection by providing to many low-quality targets for discovery. A variety of innate cell types found in the tumor microenvironment can potentially serve as APCs. The main subtypes are tumor-associated macrophages (TAMs) and tumor DCs (CD11b+ and CD103+ DCs)[77]. All subsets can interact with CTLs[99, 105], but only CD103+ DCs can efficiently reactivate T cells, leading to tumor immunity[77]. The high-quality CD103+ DCs represents only 1% of the total tumor immune infiltrate[77]. TAMs and CD11b+ DCs can therefore be considered as “obstacles”, engaging T cells and reducing the efficiency of effector T cell search to find the CD103+ cells. Like many other aspects of T cell motility, parallels can again be found in ecological models, where high target density can impair Lévy walks and promote Brownian walks, whenever encounters with targets disrupt previous directionality[106] (Box1). This concept is in agreement with the high density of non-activating APCs (CD11b+ DCs and TAMs) and the subdiffusive random migration of T cells observed in the tumor environment[77, 99].

4- Conclusion and Perspectives

T cell motility and search pattern are intertwined and it is unclear which features of T cell motility are actually important for search efficiency. Comparison of cell motility in different contexts combined with increased information about intrinsic and extrinsic parameters controlling search will be the first steps in building cell behavioral search models in order to decipher whether and how T cell search is optimized. In particular:

1) The impact of structural support and other external environment, which ranges from target densities and motility, to spatial distribution and potential obstacles.

2) The internal state of the cell.

3) The information flux 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 Brownian 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 behavioral ecology[107], but cell biology allows for an integrated comprehension of search patterns by the means of combining fundamental search theory, behaviorally-oriented search models, and real-time empirical observations (Figure 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 widely 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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Matthew F. Krummel obtained his Ph.D. at the University of Berkeley, USA, and carried out postdoctoral studies at Walter and Eliza Hall Institute, Melbourne, Australia, and Stanford University, USA, before starting his laboratory at the University of California, San Francisco, USA, in 2001. His group specializes in the study of the spatio-temporal dynamics of immune responses.

Glossary

Haptokinesis	Migration along a surface, utilizing immobilized ligand, such as chemokine or integrins, without any cue gradient to provide a directional bias.
Haptotaxis	Migration along a surface, guided by a gradient of immobilized chemoattractant or adhesion receptor ligands, providing a directional bias.

Chemokinesis	Migration driven by soluble chemokines, without any cue gradient to provide a directional bias.
Chemotaxis	Migration driven by a gradient of soluble chemokines. Directional motile response occurring when spatiotemporal asymmetries in cue reception (rate, density, etc) exists such that local cue gradients can be followed.

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Box 1

Definitions related to Search

Exploration versus Exploitation

Classic decision-making trade-off based on the amount of information available (associated with the decision). Exploitative behaviors are based on ready-to-use information. Explorative behaviors are aimed at looking for new information. In spatial searches, exploitative behaviors are typically associated with intensive (local) search and explorative behavior with extensive (as highly directional or ballistic) search, although novel search theory has started to challenge this concept (see below and [23, 24, 109]).

Random walks

1- Diffusive random walks

Random walks with no directional persistence or short-ranged (fast decaying) persistence such that the overall spreading (i.e. mean square displacement) is linear with time (see Figure below). **Brownian motion** is the limiting case of diffusive random walk.

2- Anomalous dynamics: sub- and super-diffusive random walks

Generalized random walks with sublinear (subdiffusion) or superlinear (superdiffusion) spreading (i.e. mean square displacement) with time (see Figure). Microscopic mechanisms involved in such motility patterns include speed fluctuations. A paradigmatic case of a superdiffusive walk is the **Lévy walks** characterized by a power–law move length probability distribution with finite speed and random turning directions between move lengths[87,88]. Lévy walks (and models alike[110]) are effective at randomly solving the key tension between encountering nearby and faraway targets[85,87,88,95], because they ensure a good local space-filling strategy and at the same time a superlinear overall spreading dynamics (superdiffusion) that reduces the time needed to reach distant areas. However, Lévy patterns could also emerge from informed movement and its interaction with the environment and not directly from an explorative process.

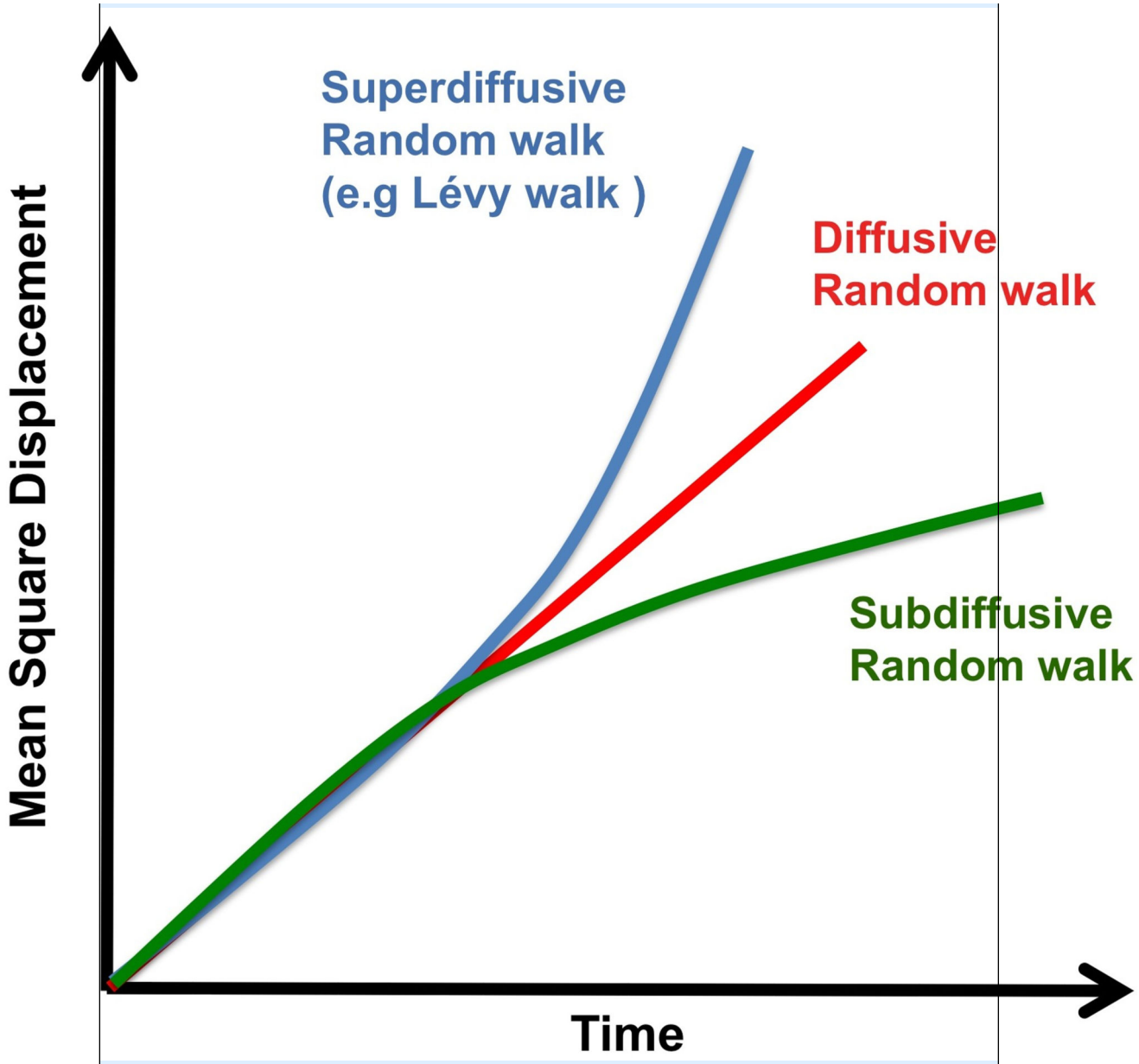

Figure. Mean squared displacement (MSD) over time for different types of random walks: diffusive, subdiffusive and superdiffusive walks

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[111]. In addition, relevant information content can be stored and used to generate effective active movement[112]. Expectation relies on the quality and nature of prior information given by the environment, and depending on such information, active search behavior might alternate between capitalizing on exploiting high-quality information and moving some distance away in order to discover new information[72]. In the field of behavioral ecology, an outstanding question is whether, at the landscape-level, movement patterns respond to exploratory behavior (less informed

movement), navigation (informed movement), or simply to the summation of locally reactive movement behavior (e.g. taxis)[113, 114]. Similarly, there is not much appreciation of the exploitative and exploratory components resulting in T cell search migration patterns.

Search theory posits two main routes to explain how search processes are optimized: (a) to have good prior knowledge (expectations) about target locations or (b) to adjust exploratory movement behavior to elementary search rules that are less reliant on cues from the environment or prior knowledge. Therefore, speed fluctuation and turning behavior are tuned to the environment considering two elementary search tradeoffs[87]: (i) the balance between speeding-up to cover larger areas and remaining slow enough to keep perception at high-performance (the so-called speed-perception tradeoff)[23, 24, 115], and (ii) the balance between thorough local exploration and the capability to spread out to new and distant areas (the so-called intensive-extensive tradeoff)[24, 39].

Bullet points

- T cells searching for their cognate APC follow similar rules and patterns to those of other biological entities, and understanding what dictates their search behavior will benefit from search theories developed in other fields.
- Search theories rely on the notion of exploration-exploitation tradeoff, for which classic decision-making are based on the amount of information available to make a decision. During an infection or insult, exploration-exploitation tradeoff changes as T cells are recruited to the response, and similarly, their patterns of migration, related to T cell search, evolves too.
- Naïve T cells looking for their cognate peptide display non-informed movements that have been described as a mix of persistent and random walk. Although their migration is guided and restricted, naïve T cells do not have any information on the localization of their cognate APC as compared to other irrelevant APCs.
- Activated and effector T cells become able to sense information coded by other relevant cells, resulting in a shift towards ‘exploitative’ motility patterns driven by chemotaxis in LNs and peripheral tissues.
- Memory T cells formed after the resolution of an immune responses conserve some expectation, as they strategically position themselves where an infection is likely to first appear, enabling them to respond to such infection more quickly than naïve T cells.
- Systems biology approaches that include search theories will be necessary to unravel essential properties and control parameters of T cell search that would lead to novel strategies to manipulate T cell responses.

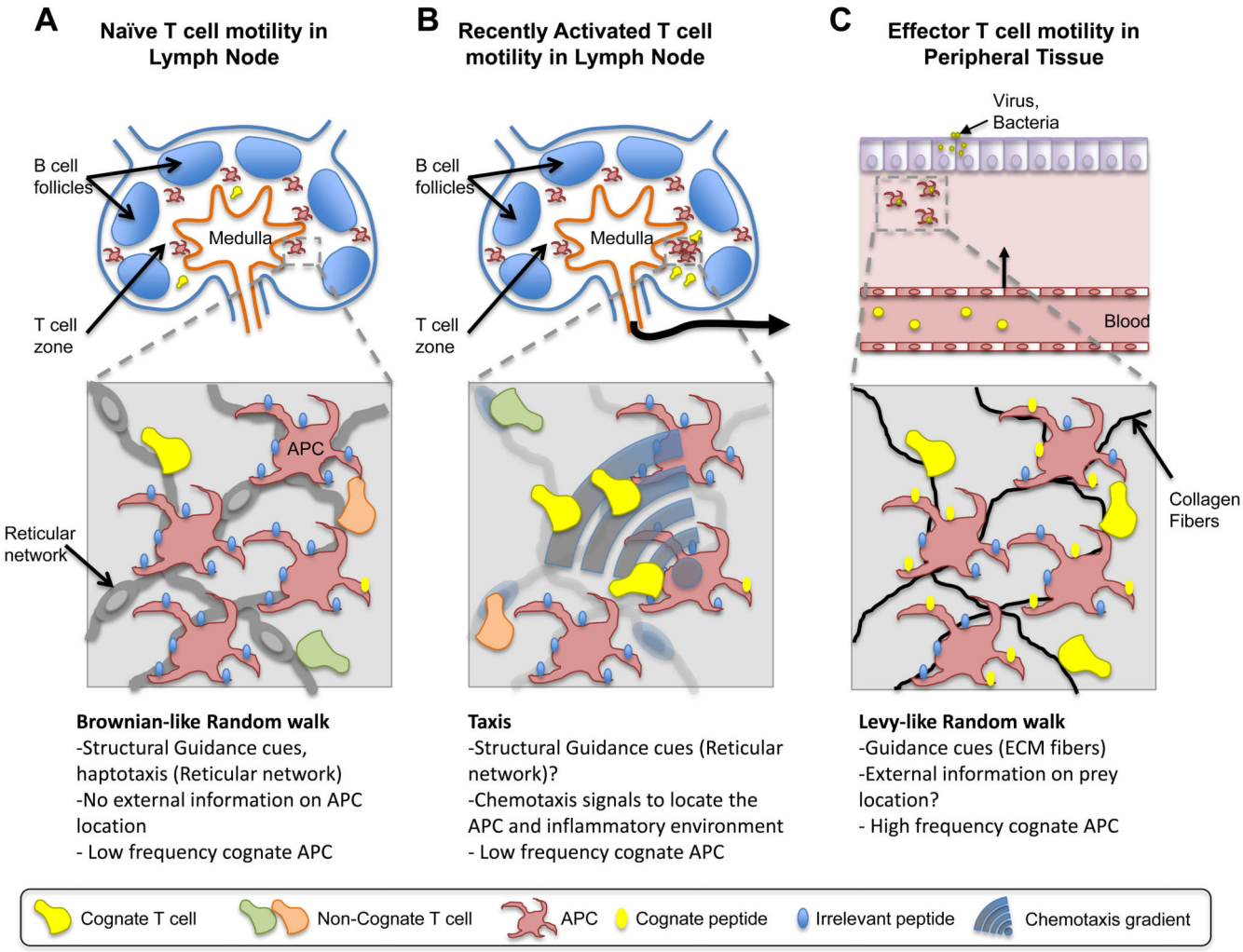

Figure 1. T cell motility according to its state of activation and the microenvironment

A- Naïve T cells migrate primarily in lymphoid organs, looking for their cognate peptide (in yellow) presented by an APC. The frequency of the cognate APC within the midst of APCs is extremely rare, and there is no information on the location of the cognate APC. Naïve T cells in lymph nodes use a diffusive (e.g. Brownian-type) or subdiffusive random walk. T cell migration is in part cell-autonomous, supported by guiding stromal structures and relies on chemokinesis.

B- The location of Recently activated T cells, i.e T cells that found their cognate peptide, is restricted to the secondary lymphoid organ in which they got primed. However, their migration is now directionally biased. Chemotaxis signals are sent by the cognate APC, most likely to attract recently activated T cells to a distinct differentiating environment.

C- Once primed T cells efficiently differentiate in effector T cells, they leave secondary lymphoid organs to reach the site of injury in peripheral tissues. Within this tissue, effector T cells will have to find their cognate APC again during antigen reencounter. Depending on the tissue and injury, effector T cell migration in peripheral sites has been described as a diffusive (e.g. Brownian-type) or superdiffusive (e.g. Lévy-type) random walk.

Haptokinesis, haptotaxis and chemotaxis have been shown to shape this walk in some tissues.

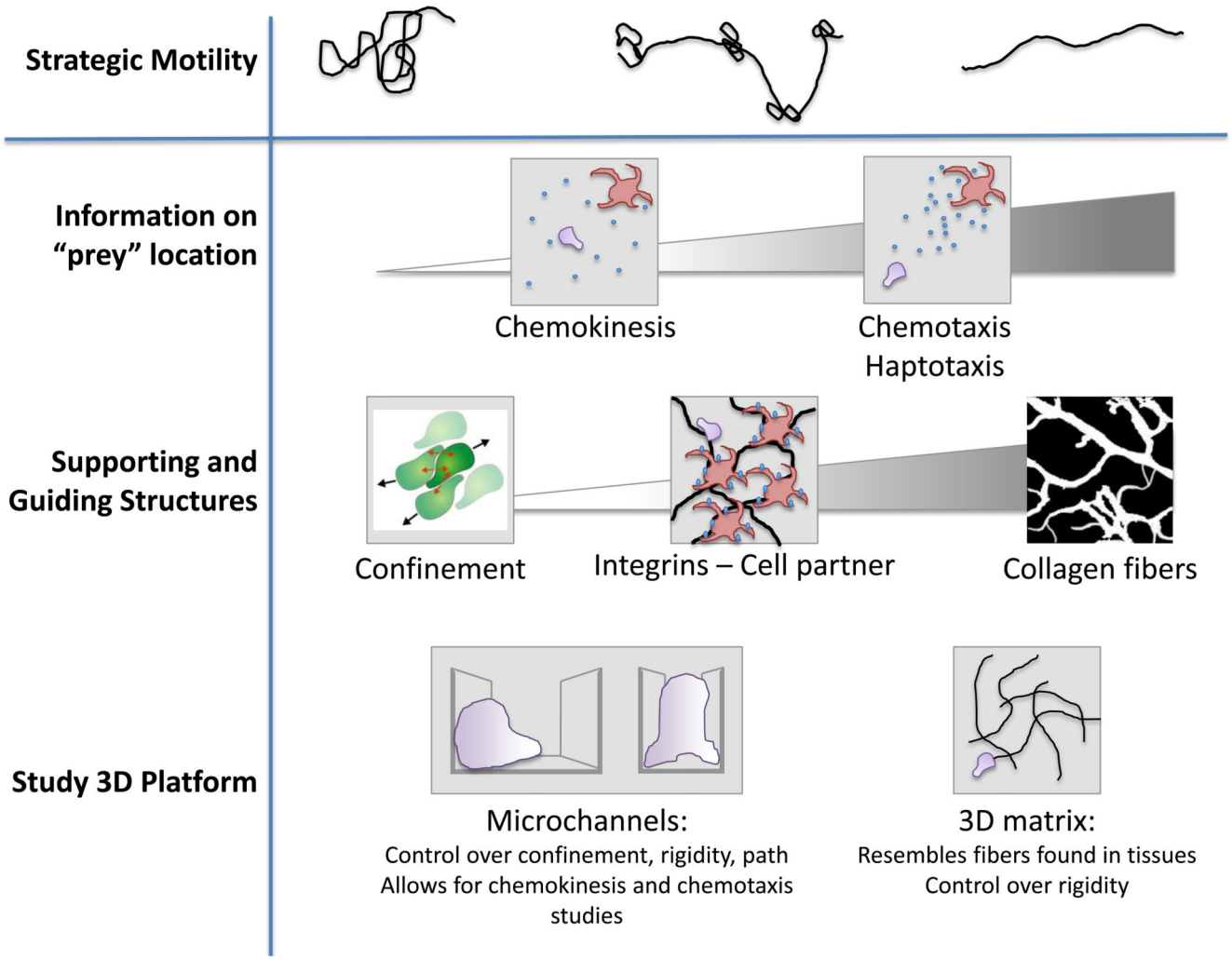

Figure 2. Factors influencing T cell motility features and platforms used to study T cell migration characteristics

Figure describes the different T cell motility behaviors, from normal (Brownian-type) (left) to ballistic (highly directional) (right) passing through anomalous (superdiffusive) regimes and the different factors that are known to dictate this behavior. Strategic motility is influenced by cell-autonomous features, as well as environmental guidance structures, which include confinement, chemokinesis and haptokinesis. Depending on the pattern of the guiding structures themselves, directional bias will be observed. Strategic motility will also be influenced by the APC itself. In particular, the frequency and location of cognate APCs in relationship to total APCs and the signals they send out to be found (mainly integrins and chemokines) will affect T cell motility patterns. In this context, chemotaxis will efficiently promote directional T cell migration. Finally, different platforms can be used to study features of T cell motility, each platform allowing for the study of specific migration parameters. Microchannels allow for the study of cell-autonomous migration, confinement, chemokinesis or chemotaxis. 3-Dimension (3D) matrices resemble fibers found in tissues and allow control over rigidity and chemotaxis studies.

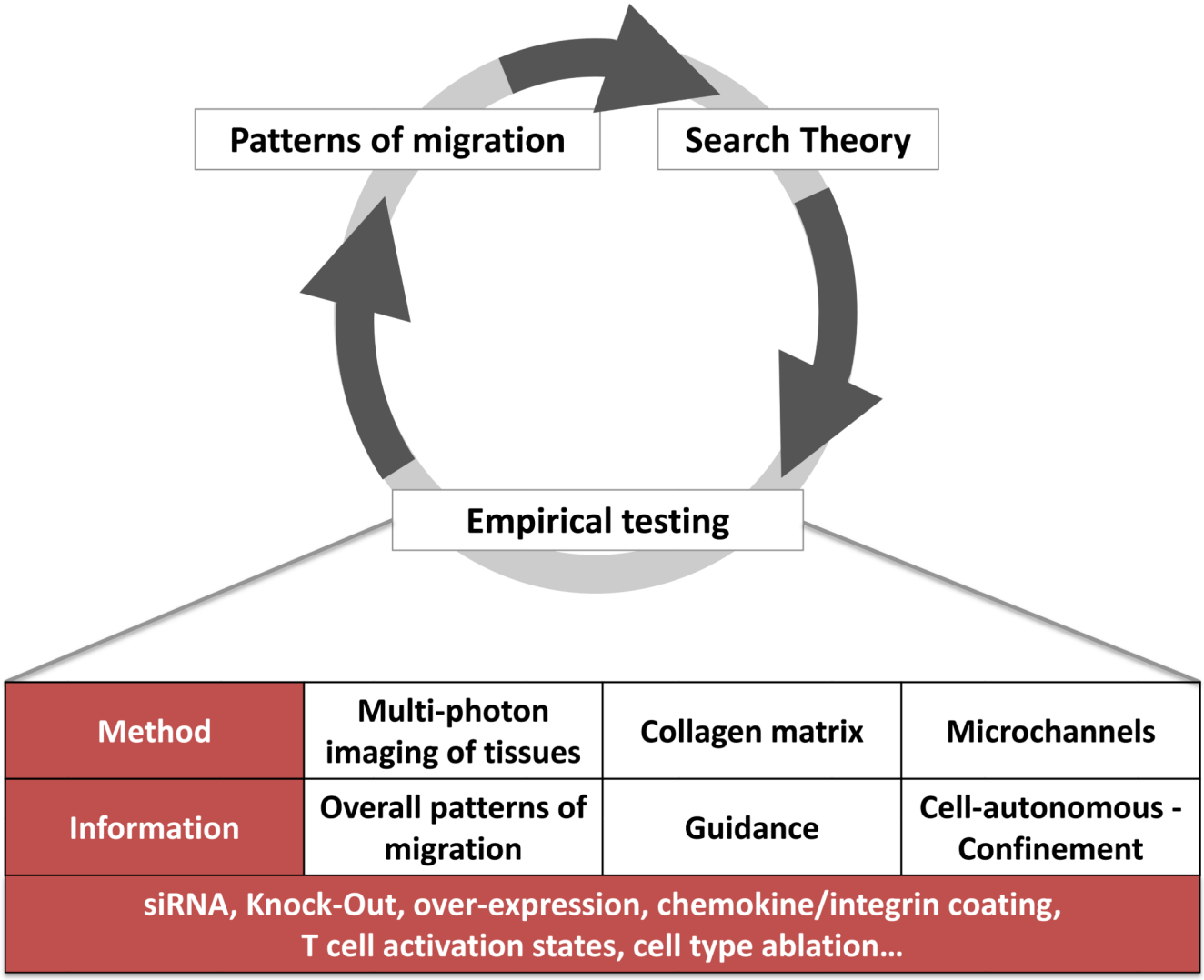

Figure 3. System biology and integrated studies to unravel search in biology

Figure describes how the integration of current search theories, empirical testing and the analysis of patterns of migration are necessary to understand what governs cell migration and how it relates to search efficiency.