

# “If you please... draw me a cell”. Insights from immune cells

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## ABSTRACT

Studies in recent years have shed light on the particular features of cytoskeleton dynamics in immune cells, challenging the classical picture drawn from typical adherent cell lines. New mechanisms linking the dynamics of the membrane–cytoskeleton interface to the mechanical properties of immune cells have been uncovered and shown to be essential for immune surveillance functions. In this Essay, we discuss these features, and propose immune cells as a new playground for cell biologists who try to understand how cells adapt to different microenvironments to fulfil their functions efficiently.

## Introduction

“If you please... draw me a sheep”. Lost in the desert, you would have little difficulty drawing a sheep if the Little Prince asked you to. However, you might find it more difficult if he were to ask: “If you please... draw me a cell.” You might hesitate, depending on your background, as cells from multicellular organisms have diverse shapes and properties. If you had studied cancer-derived epithelial or fibroblast cell lines, you might draw a flat fried-egg-shaped adherent object. Alternatively, you might draw an *in situ* epithelial cell; rectangular, static and polarised. Immunologists would be more likely to draw a polarised, potentially motile cell, probably without focal adhesion, possibly a phagocytic or macropinocytic cell. It is even harder to draw ‘a’ cell in the *in vivo* context, as cells from multicellular organisms reside in tissues with different physical and chemical properties that can influence cell behaviour. These observations led us to wonder what immunologists and cell biologists can learn from each other.

In multicellular organisms, most cells reach their final positions during embryonic development, and then fulfil their function at that site, or at least within the same tissue. An ability to migrate and to change their microenvironment is often considered a pathological hallmark of cancer cells, but immune cells also have these properties. What makes immune cells special is that each individual single immune cell can migrate between tissues, fulfilling specific functions in different microenvironments. To be able to do this, immune cells must be able (1) to explore multiple environments (i.e. migrating in search of a danger signal originating from a pathogen or another cell), (2) to gather and/or transmit information, generally by secreting cytokines or through direct cell–cell contact via an ‘immune synapse’ and (3) to exert effector functions, by eliminating the pathogen such as through phagocytosis (macrophages and neutrophils), killing dangerous cells [cytotoxic T cells and natural killer (NK) cells] or secreting antibodies (B cells).

In this Essay, we will highlight the unusual features of immune cells relative to typical ‘textbook’ adherent cells, focusing particularly on their cytoskeleton dynamics and cell mechanics. We also propose that, thanks to their unique properties, immune cells were selected during evolution to operate at spatial and temporal scales different from those of typical adherent cells.

## Immune cells continually change morphology and polarity

Most cells acquire their overall shape early during development and do not undergo major shape changes, at least over short time scales (minutes). For example, neurons may grow and their synaptic connections may change during their lifetime, but they retain the same overall morphology. The maintenance of cell shape is dependent on interactions between cells, which are regulated by junction molecules, such as cadherins, or on signals generated by interactions with the extracellular matrix, which contains adhesion molecules, such as integrins (Lecuit and Lenne, 2007). The most unusual feature of immune cells is, thus, their continually changing morphology, enabling them to adapt to the physical and biochemical features of the environments with which they come into contact. This ability is dependent on a highly dynamic actin cytoskeleton, the presence of which makes these cells an ideal model for cell biology studies.

Immune cells can change shape very rapidly. For instance, lymphocytes become elongated during migration with their shape tightly coupled to their speed (Hons et al., 2018), but they round up again within seconds upon immobilisation (Dustin, 2008). It remains unclear what triggers the rounding of immune cells when they stop migrating, but  $Ca^{2+}$  signalling has been implicated in T cells (Donnadieu et al., 1994; Dustin et al., 1997; Negulescu et al., 1996). Cell rounding may also occur very rapidly during the division of adherent cells. In this case, cell rounding is accompanied by a strong increase in cortical tension, allowing the cell to withstand the compressive stress of the surrounding tissue (Kondo and Hayashi, 2013; Théry and Bornens, 2008). We can therefore hypothesise that the changes in cell shape of immune cells depend on the environmental stresses they face at a given time. What is the machinery that helps immune cells rapidly respond to external cues by reshaping? First, immune cells are the smallest and softest of all mammalian cells (together with metastatic cells!) (Bufi et al., 2015). Their relatively low rigidity may facilitate rapid and efficient changes in shape and mechanical (microrheological) properties. Interestingly, neutrophils have been recently reported to stiffen and shrink upon activation and then expand and soften again within minutes (Bashant et al., 2019). Modification of rheological properties have also been observed upon antigen recognition in both B and T cells (Zak et al., 2019, preprint). Second, under the microscope, most immune cells can be seen to be covered with microvilli, which constitute a major source of membrane material for rapid shape changes (Cai et al., 2017; Jung et al., 2016; Majstorovich et al., 2004; Shao et al., 1998). The formation and stabilisation of microvilli depend on the physical properties of the membrane mediating the local reorganisation of actin-associated

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proteins and nucleators. Microvilli are present in several different types of immune cells, but have different dynamics in different cells.

Morphological changes are not restricted to the shape of the cell, but also concern its internal components. Developing tissues typically rapidly establish a polarity pattern (Cowan and Hyman, 2007), and most polarised cells, such as epithelial cells and neurons, do not change polarity during their lifetime. Indeed, cell polarity is often dependent on the microenvironment, and, as this environment tends to be stable for most cells, polarity is maintained over the lifespan of the cell (Gundersen and Worman, 2013). By contrast, the polarity of immune cells is continually challenged – while migrating in response to biochemical or mechanical cues and when polarising towards a cell to establish a synapse, or re-orienting to break the contact and follow another signal.

Below, we explore the role of changes in shape and polarity on the various functions accomplished by immune cells.

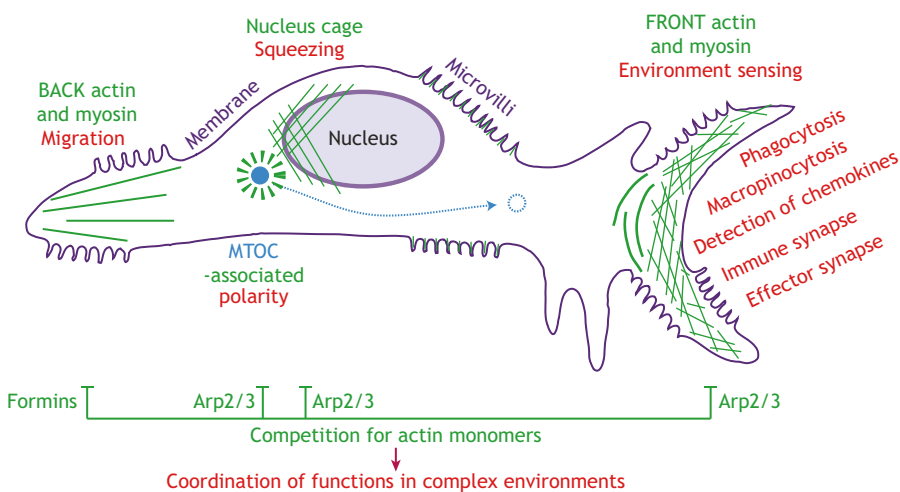
**Immune cells migrate with minimal forces in complex environments**

Another remarkable feature of immune cells is their ability to migrate. Classical textbook cells (e.g. HeLa cells) migrate through adhesion of their front end to the substrate, followed by pulling on the adhesion molecular ‘clutch’ to move forward. However, they need to release the clutch at some point to keep moving forward (Hu et al., 2007). Strikingly, immune cells migrate mostly without integrin-mediated adhesion (Friedl et al., 1998; Lämmermann et al., 2008). Their migration process is similar in this respect to that described for *Dictyostelium* (Friedl and Wolf, 2010), and this mode of migration is therefore described as amoeboid. This has been observed in confined environments *in vitro* and *in vivo*, and it enables immune cells to navigate through tissues for the purposes of immune surveillance.

Amoeboid migration depends on a particular organisation of the building blocks of the cytoskeleton, particularly those controlling actin nucleation and actomyosin contractility (Chabaud et al., 2015; Jacobelli et al., 2009; Jacobelli et al., 2010). This type of migration is particularly efficient in confined environments, such as the interstitial space in tissues, in which immune cells move. The immune cell cytoskeleton is reorganised to generate forces that squeeze the cell, and particularly its nucleus, through constrictions (Lämmermann et al., 2008; Raab et al., 2016; Thiam et al., 2016; Wolf et al., 2013). Dendritic cells migrating in constricted conditions generally have three pools of actin: one at the front and

one around the nucleus, which both show branched filaments that are nucleated by the Arp2/3 complex, and the final one at the back comprising actin bundles, nucleated by formins. The first drives macropinocytosis (i.e. environment sampling), the second squeezes the nucleus through constrictions (e.g. collagen pores or cell–cell junctions), and the third propels the cell forwards (Fig. 1). Myosin II at the back of the cell is thus involved in squeezing and propelling the cell, whereas the myosin II at the front of the cell promotes macropinosome maturation and the transfer of macropinosome content to lysosomes (Bretou et al., 2017; Chabaud et al., 2015).

Adherent migration requires the generation of strong forces, which may slow the cells down. By contrast, non-adhesive modes of migration make use of frictional forces against the substrate. The ranges of stress generated by these two types of migration are very different [ $\sim 100$  Pa for adhesion-mediated migration versus less than 1 Pa for cortical flow-driven migration (Bergert et al., 2015)]. The generation of smaller forces does not result in slower migration, because the cells do not need to detach from the substrate to move forward (Lämmermann and Sixt, 2009). They have indeed less effective friction to overcome. They can even simply use the topography of the substrate to propel themselves, in the absence of any molecular link between the cytoskeleton and the substrate (Reversat et al., 2019, preprint). During interstitial migration, the generation of small forces acting against the environment may enable immune cells to detect weak environmental cues and to integrate local chemical and mechanical signals. For instance, neutrophils are able to follow the minimal hydraulic resistance path (barotaxis), thereby overriding chemotactic signals (Prentice-Mott et al., 2013). Conversely, immature dendritic cells overcome barotaxis by performing macropinocytosis, enabling space exploration; this feature is lost upon maturation, allowing mechanical (and not only chemical) guidance to lymph nodes. Barotaxis appears to not depend on any specific molecular sensor but rather to be the result of intrinsic properties of the actomyosin cytoskeleton (Moreau et al., 2019), suggesting that any cell is subjected to barotaxis, except cells that are endowed with an efficient fluid transport mechanics, such as immature dendritic cells and macropinocytic metastatic cells. During extravasation, immune cells must counteract flow; they therefore need to generate more force, through integrin-mediated adhesion, which they achieve by changing their motility mode (Shulman et al., 2009; Sixt et al., 2001).



**Fig. 1. Draw me an immune cell.** Artistic view of the different actin pools and associated functions in immune cells. Green text indicates actin pools, and red text associated functions. The actin pool at the back (organised into cables, formin-mediated) is responsible for amoeboid cell migration, the pool around the nucleus (branched, Arp2/3 mediated) is responsible for translocation through constrictions, and the pool at the front (branched) is responsible for macropinocytosis, phagocytosis, environment sensing and the formation of the immune synapse. Actin has been found around the microtubule-organising center (MTOC), playing a role in the polarisation of this structure. Competition for actin monomers acts as a switch between different functions.

### Immune cells actively patrol their environment and test their local surroundings and neighbours

Cells in tissues depend on external factors (nutrients, growth factors, etc.) to survive. They sense these factors at the plasma membrane, or actively take them up. Immune cells use a similar strategy to sense their environment. Cytokines are sensed directly by membrane receptors, providing local information. However, immune cells often collect information over a whole tissue, or even across the whole body. They are therefore highly dependent on cell migration, as described above, to gather broadly distributed information, as well as on the local environment and cell scanning.

During migration, immune cells often undergo repolarisation, for instance to change direction, avoid obstacles or follow chemokine gradients. These repolarisation events occur over very short time scales (Schumann et al., 2010). Gradients of chemical signals (chemotaxis) provide a good trail to targets that is widely exploited in bacteria (Berg and Purcell, 1977). Immune cells make use of a similar mechanism, haptotaxis, that is, the following of gradients of immobilised molecules, in which their orientation accuracy is precisely dependent on the signal:noise ratio of the chemokines (Schwarz et al., 2017; Weber et al., 2013). Cell polarisation occurs through a biasing of actin polymerisation following the engagement of the chemotactic receptor (a system that is radically different from the run-and-tumble in bacterial chemotaxis). Actin-driven protrusions, such as lamellipodia, in particular, are thus highly efficient detectors of haptotactic gradients, but they are dispensable, as discussed above, for locomotion (Leithner et al., 2016). Physical obstacles can also drive cell orientation, due to the load dependence of actin polymerisation. Greater compression of the actin network (by an obstacle) results in a stiffening of this network, generating a force that acts against the compression (Mueller et al., 2017). Recently, the nucleus has been suggested to guide the cell towards the largest pore size, minimising mechanical resistance to migration (Renkawitz et al., 2019).

Environmental patrolling is optimised not only by control over the direction of movement and its guidance by physico-chemical cues, but also by the coordination of migration and microenvironment testing. This rather general mechanism renders immune cells incredibly efficient at sensing their microenvironment, collecting information and transmitting it to other cells, and at fulfilling their effector functions. In dendritic cells, for example, the uptake of large amounts of fluid through macropinocytosis for environmental scanning is antagonistic to migration. This antagonism results from the dependence of amoeboid migration and macropinocytosis on the same cytoskeleton building blocks, essentially the key player of actin contractility, myosin II, which is diverted from the back to the front of the cell to contract macropinosomes (Fig. 1) (Lavi et al., 2016). As a result, dendritic cells display intermittent searching activity, with an alternation of locomotion and sensing phases (Faure-André et al., 2008). This strategy has been shown to be efficient for the sampling of sparse targets (Bénichou et al., 2011). The rate of switching between locomotion and sensing is optimised for the detection of a signal within hours over distances of several hundreds of microns, consistent with *in vivo* observations (Chabaud et al., 2015).

In general, cells in continuous motion also move very fast, their polarisation being reinforced by the retrograde actin flow responsible for locomotion itself. Consistently, the contractile machinery (myosin II) is also more polarised at the back of the cell in the fastest and most persistent cells (Chabaud et al., 2015). More recently, spontaneous actin waves have been shown to generate the polarity cues and hence determine the diffusive versus persistent

dendritic cell migration (Stankevicius et al., 2020). Immune cells spontaneously change polarity as a consequence of cortex instability or their differentiation and/or activation state. The alternation between low- and high-persistence states can be explained by the competition between the nucleation machineries for actin monomers (Fig. 1). This may help immune cells to build dynamic actin pools at different cellular locations, facilitating rapid repolarisation. Intermittent migration requires the coordination of migration and function and leads an optimal environmental patrolling (Chabaud et al., 2015; Lavi et al., 2016). Accordingly, mature dendritic cells, whose main function is efficient migration to the lymph nodes to initiate immune responses, rather than tissue patrolling, lose the ability to engage myosin at their front. The actomyosin machinery therefore remains at the back of these cells, resulting in a downregulation of macropinocytosis, but promoting the continual rapid locomotion of these cells (Vargas et al., 2016). Interestingly, T lymphocytes have also been reported to display intermittent migration, and appear to require the atypical motor protein myosin IG (Gérard et al., 2014).

The local microenvironment is also tested by the constant scanning of neighbouring cells, as exemplified by T cells continually searching for their antigens. At a microscopic scale, these processes are dependent on dynamic membrane structures, such as protrusions, villi or ruffles (Fig. 1). These structures are mostly constitutive but can also be reinforced by specific signalling (Pollard and Cooper, 2009). For example, lymphocyte microvilli are connected to specific signalling platforms and, at least for T cells, have been shown to scan the interaction area with another cell within seconds and then make a decision within one minute (Brodovitch et al., 2013). The efficiency of this scanning process was recently reported to be dependent on the structure and dynamics of microvilli (Cai et al., 2017), actin-filled protrusions that move actively at the surface of T cells, thereby maximising surface coverage and minimising mutual overlap. Microvilli have a residence time of 3–6 s in the absence of ligand. Once specific contact between the T cell receptor (TCR) and its ligand has been established, the individual microvilli are stabilised, potentially owing to TCR–ligand catch-bond behaviour (Pullen and Abel, 2019), allowing amplification of the signal and antigen discrimination. Remarkably, microvilli have been also shown to release TCR-enriched vesicles and transmit information to antigen-presenting cells (APCs) (Kim et al., 2018).

### Immune cells gather and transmit information through synapses

When an immune cell finds a cognate partner, it can establish contact with this other cell through the so-called immunological synapse. This structure owes its name to the neurological structure, as both types of synapse mediate the direct transfer of information from one cell to another, and they have also been shown to have a similar organisation. In the immunological synapse, the lymphocyte and the APC (or lymphocyte and target cell) (1) adhere to each other via a lamellipodium-like structure, (2) are reorganised into a centrosymmetric configuration, with antigens located at the centre and adhesion molecules at the periphery, and (3) subsequently detach from each other to resume their migration. Immune synapses are associated with various immune cell activation events, including antigen internalisation (in B cells), cell proliferation and the secretion of cytokine-containing vesicles (CD4<sup>+</sup> T cells) or other molecules required for effector function, for cytolysis in the case of CD8<sup>+</sup> T cells and NK cells, for example.

Immune synapses form and break down again within minutes. How can such drastic shape changes and molecular reorganisation

occur so fast? Rapid shape changes make use of specific signalling cascades that amplify the primary signal, leading to a downstream reorganisation of the cytoskeleton building blocks within minutes. In the case of the immune synapse, antigen recognition by specific receptors (TCRs or BCRs) triggers a cascade involving kinases, such as p21-activated kinase (PAK) and phosphatidylinositol 3-kinases (PI3Ks), and small GTPases (e.g. Cdc42, Rac2 and Vav), that ultimately remodel the actin cytoskeleton. In particular, a domination of Wiskott–Aldrich Syndrome protein (WASP) activity over protein kinase C  $\theta$  (PKC $\theta$ ) has been reported to be crucial in T cells to ensure the symmetry and stability of the immune synapse through a fine control of actin polymerisation at the synapse (Sims et al., 2007). This stabilisation relies on an intracellular in-plane tension that is sustained at the synapse by WASP-dependent actin nucleation at TCR microclusters and interaction with Myosin-II. WASP degradation leads to a release of cytoskeletal tension and synapse breaking (Kumari et al., 2020). WASP might also regulate receptor mobility in activated B cells (Rey-Suarez et al., 2020). Signalling at the immune synapse further stimulates the local actomyosin reorganisation into a centripetal flow driven by contractile arcs that are stretched by radial actin bundles (Yi et al., 2012). Like the pools of actin in migrating dendritic cells, the two classes of filaments are regulated by different nucleators (Arp2/3 versus formins), making it possible to group clusters of receptors together at the synapse (Murugesan et al., 2016). Super-resolution techniques have shown the presence of a third central ramified network in between the immunological synapse and the nucleus, which might be involved in intracellular transport of TCRs (Fritzsche et al., 2017). Whether this actin pool is similar to the actin cloud that tethers the microtubule-organising centre (MTOC) to the nucleus of lymphocytes remain to be established (Obino et al., 2016).

The rapidity of these signalling events and the subsequent responsiveness of immune cells may also be facilitated by their small size (large area:volume ratio) and the patterning of their membrane, which has been little studied. Indeed, these features might allow signals to be transduced rapidly from the membrane to the cytosol, as membrane compartmentalisation has been reported to accelerate chemical reactions and to improve control over these reactions. In addition, decreasing dimensionality speeds up reactions. These general membrane properties combined with the underlying cytoskeleton dynamics favour aggregation and stabilise receptor clustering (Gowrishankar et al., 2012; Su et al., 2016). These particular signalling properties render immune cells highly responsive to extracellular signals and, therefore, very versatile.

The specific encounter between lymphocytes and APCs modifies their ‘environment’, resulting in changes to both cell shape and cell polarity. During immune synapse formation, the entire network of microtubules (and hence the MTOC) is re-oriented towards the site of cell–cell contact (Fig. 1). This polarity axis then reverts to its original state when the cells break contact and resume their migration (Sims et al., 2007). During proliferation, in particular, lymphocytes eventually undergo asymmetric cell division along the axis putatively established during cell–cell contact (Barnett et al., 2012; Chang et al., 2007; Thauinat et al., 2012). This regulates the differentiation of T lymphocytes into memory cells, and lymphocyte polarity thus appears to determine their fate. Ancestral polarity mechanisms (typically the Cdc42–aPKC–PAR3/6 axes) that are common to most polarised cells are also at work in immune cells (for reviews, see Krummel and Macara, 2006; Russell, 2008; Yuseff et al., 2013). However, immune cells and the cells that form tissues differ in the speed in which polarity changes occur (Reversat et al., 2015; Yuseff et al., 2011). The rapid changes

in polarity observed in immune cells may be due to a particular feature of the cytoskeleton, that is the high capacity of their centrosome to nucleate actin (Farina et al., 2016; Obino et al., 2016). In B lymphocytes, F-actin is nucleated by Arp2/3 at the centrosome and this nucleation decreases upon lymphocyte engagement, probably due to Arp2/3 recruitment to the immune synapse. The downregulation of actin nucleation at the centrosome facilitates its physical detachment from the nucleus, allowing its rapid polarisation to the synapse (Fig. 1). Actin recruitment to the centrosome has recently been shown to depend on the small protein HSBP1, which promotes the local assembly of the actin nucleator WASH at the centrosome (Visweshwaran et al., 2018).

Immune cells have played an instrumental role in improving our understanding of the role of mechanical aspects in the fine sensing of the cell environment. Immune cells may use mechanical mechanisms to steer their migration (see above), and in interactions with other cells. Antigen recognition triggers macroscopic forces at the T cell synapse (Hui and Upadhyaya, 2017; Husson et al., 2011). More locally, at the B cell synapse for example, the rate of loading on the receptor (its pulling speed) mediates affinity-based discrimination between antigens (Natkanski et al., 2013; Spillane and Tolar, 2016). In T cells, the force experienced by the TCR at the synapse is independent of antigen affinity owing to adaptation of the actin flow (Colin-York et al., 2019). In cytotoxicity synapses, forces are generated that increase cell adhesion and the efficiency of perforation (Basu et al., 2016). Interestingly, the TCR responds as a catch bond (Liu et al., 2014), which increase affinity for the ligand when pulled apart from it. It remains unclear what effect this has on T cell biology and whether similar mechanisms may be at work in other lymphoid cells. More generally, mechanosensing plays a key role in cell-to-cell communication within the immune system. The properties of the actin cortex are modified by the inflammatory state of the immune cell (Bufi et al., 2015), and signalling is closely related to the rigidity of the substrate with which the cell interacts (Judokusumo et al., 2012; O’Connor et al., 2012; Saitakis et al., 2017; Shaheen et al., 2017). Similarly, B cells have been recently shown to protrude actin-rich structures where antigens are extracted when contacting soft substrates, that is whose stiffness matches the one of APCs (Kumari et al., 2019). Formation of such protrusions involve both Arp2/3 and formins (Bolger-Munro et al., 2019; Kwak et al., 2018; Roper et al., 2019) and resemble those previously described in CD4<sup>+</sup> T cells (Sage et al., 2012). The function of the immunological synapse (both B-cell–APC and T-cell–APC) therefore relies on coordinated actin structures that display distinct organisations and subcellular localisations and are regulated by the physical properties of APCs. These different actin pools might be unique to immune cells or, alternatively, be related to the actin structures extensively characterised in adherent cells such as focal adhesions, podosomes and invadosomes, and could therefore be used to learn more about their regulation.

### Conclusion – immune cells as a new playground for cell biologists

As discussed here, the highly dynamic properties of the cytoskeleton–membrane interface of immune cells allow these cells to modify their shape, polarity and locomotion in response to environmental cues and to fulfil their function. They also make these cells a powerful study model, and studies of these cells have recently challenged a number of classical cell biology concepts developed from studies of adherent cell lines. Immune cells have a number of features in common with cancer cells. Do the particular

features of immune cells also observed in cancer cells facilitate the spread of these cells to healthy tissues? Some of the analogies between the two cell types appear particularly pertinent: first, cancer cells become highly migratory, like immune cells, and second, cancer cells also often become macropinocytic, enabling them to take up huge amounts of extracellular nutrients to satisfy their high metabolic needs (Commisso et al., 2013). Do these similarities result from similarities in cytoskeletal and biophysical properties between immune cells and cancer cells? To what extent are these two sets of cells similar and how do they differ?

The most crucial characteristic of immune cells is probably the efficiency with which they perform particular functions. Most of the mechanisms described above have also been observed in other systems, but they have been explicitly linked to optimal behaviour in immune cells: optimal rates of switching between locomotion and sensing, optimal numbers and dynamics in environmental scanning by microvilli, optimal loading rate and the force for discriminating antigens. This tight control over their cellular functions makes immune cells good models for studies of fundamental cell biology and cell mechanics. Unfortunately for the Little Prince, it isn't really possible to draw a stereotypical cell. Cell biology is far too complex to be captured in a simple sketch. Maybe, as for the sheep in *le Petit Prince*, it is best to draw a box and leave biologists to continue exploring what is hidden inside!

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#### Competing interests

The authors declare no competing or financial interests.

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