Cell migration in Immunology

The right cell(s) to the right time at the right place

Dr. Stefanie Gnipp
1. General introduction

2. How do the leukocytes leave the bloodstream and enter the tissue?
   - vascular trespassing/extravasation
   - molecular process

3. How do the leukocytes move within the tissue?

4. Cell motility and cell shape remodeling

5. How do the cells know that and where they have to migrate?
   - Soluble signals: Chemokines

6. Diseases associated with defective cellular locomotion
The *movement*, or *migration*, of cells (also known as *cell motility*) is an important part of many biological processes. Cell migration is observed in immune cells, during embryonic development, wound repair and in the formation of new blood vessels (a process known as angiogenesis).

**Further:**
- placental development (trophoblast invasion)
- cancer; metastasis
The trafficking of leukocytes into and within lymphoid and peripheral tissues is central to immune cell development, immunosurveillance and effector function. Interstitial leukocyte trafficking is the result of amoeboid polarization and migration, guided by soluble or tissue-bound chemoattractant signals for positioning and local arrest.
Cell trafficking in immunology

Effector function

"physiologic"
Infection
Injury

immune homeostasis

pathologic
Autoimmune diseases
Hypersensitivity
Cancer/Immunodeficiency

\[ \text{CNS} \]
\[ \text{Air space} \]
\[ \text{Neuron} \]
\[ \text{Monocyte} \]
\[ \text{Th1} \]
\[ \text{Th2} \]
\[ \text{B} \]
\[ \text{PMN} \]
\[ \text{CCL6, CCL7, CCL8} \]
\[ \text{CXCL10, CXCL11} \]
\[ \text{CXCR1, CXCR2} \]
\[ \text{CCL25 (CCR10 ligand)} \]
\[ \text{CCL3, CCL4, CCL5} \]
\[ \text{CCR1, CXCR3} \]
\[ \text{ICAM-1} \]
\[ \text{LFA-1} \]
\[ \text{PSGL-1} \]
\[ \text{LTB4 (BLT1 ligand)} \]
\[ \text{Tg2} \]
\[ \text{MC} \]
\[ \text{CCR3} \]
\[ \text{MC} \]
\[ \text{LTB4} \]
\[ \text{T} \]
\[ \text{Th1} \]
\[ \text{Th2} \]
\[ \text{CCL7 (CCR10 ligand)} \]
\[ \text{CCL1, CCL2, CCL3, CCL4} \]
\[ \text{CCR5, CCR6} \]
\[ \text{CCR11, CCL11} \]
\[ \text{CXCR1, CXCR2} \]
\[ \text{LTB4} \]
\[ \text{Th1} \]
\[ \text{Th2} \]

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Both innate and adaptive immune functions depend upon interstitial leukocyte migration.

After leaving the bone marrow by way of the blood, monocytes and granulocytes reach lymphoid or peripheral tissues, move toward their targets and execute effector functions.

Dendritic cells (DCs) collect and process antigenic material and, in response to maturation signals, migrate from the periphery to lymphoid tissues to present antigens and trigger T cell activation.

T lymphocytes emigrate from the thymus, become activated by a cascade of cell-cell interactions in secondary lymphoid organs and circulate to peripheral tissues for effector function.

Similarly, B lymphocytes move within secondary lymphatic tissues to capture antigen, receive T cell help and recirculate and become resident in the bone marrow and other lymphoid organs as antibody-secreting plasma cells.
How do the leukocytes leave the bloodstream and enter the tissue?

How do they know where they have to leave the circulation?
Cell trafficking in immunology

Scenario: Inflammation

1) Infectious agents: release of PAMPs (*pathogen associated molecular patterns*)
2) Tissue damage: release of DAMPs (*damage associated molecular patterns*)

- resident cells of the innate immune system (mast cells; macrophages; DCs..)
  release of pro-inflammatory mediators/Cytokines

- activation

- endothelial cells (microvasculature)

Molecular changes: (E- and P-Selectin expression on surface) enables recognition by circulating leukocytes and recruitment to inflamed tissue
vascular trespassing/extravasation of leukocytes

Overview

The recruitment of leukocytes from the circulation into tissues is a multistep cascade:

1. Slow down velocity in the blood flow (selectin-dependent)= capture
2. movement on the vascular wall= rolling
3. Stimulation by sense signals, presented by the endothelium= activation
4. cell adhesion to the apical endothelial plasma membrane= adhesion
5. crawling through the endothelium into the underlying tissue= transmigration/ diapedesis
6. Migration within tissue
vascular trespassing

capture and rolling: selectin-mediated

- Selectins mediate the capture from bloodflow >> slowing down velocity
- transient interaction / bloodflow >> rolling movement of cells
vascular trespassing/extravasation

Molecular principles

**Selectins:**
- Expression on endothelial cells upon activation
- P-Selectin = „platelet“ selectin
- E-Selectin = „endothelial“ selectin

**Integrins:**
- *trans-membrane receptors* that mediate dynamic interactions between the extracellular matrix and the actin cytoskeleton during cell motility
- αβ heterodimers with a large extracellular domain that binds the extracellular matrix (ECM) and links to the actin cytoskeleton through a short cytoplasmic tail
- Binding specificity is determined by the extracellular domain of integrins that recognize diverse matrix ligands including fibronectin, collagen and laminin
- They recognize cell surface receptors including the Ig superfamily members **ICAM-1** (by LFA1: αLβ2, αMβ2) or **VCAM-1** (by VLA4:α4β1)

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Adhesion upon activation (Chemokine..!)
vascular trespassing/extravasation
alternative ways: paracelluar vs. transcellular

Figure 3. Transmigration. Migration of leukocytes through vascular walls involves penetrating the endothelial cell barrier and its associated basement membrane and the pericyte sheath. a | Extension of leukocyte membrane protrusions into the endothelial-cell body and endothelial-cell junctions is triggered by ligation of intercellular adhesion molecule 1 (ICAM1) by MAC1 (macrophage antigen 1). Ligation of ICAM1 is associated with increased intracellular Ca\(^{2+}\) and activation of p38 mitogen-activated protein kinase (MAPK) and RAS homologue (RHO) GTPase, which may collectively activate myosin light-chain kinase leading to enhanced endothelial-cell contraction and hence opening of interendothelial contacts. These events may promote leukocyte migration through endothelial junctions (paracellular route), although leukocyte migration may also occur through the body of the endothelium (transcellular route). Transmigration through the endothelium can also induce cell-surface expression of members of the β₂-integrin family and promotes on neutrophils and other leukocytes that may facilitate the outwards movement of the leukocyte through the vessel wall. b | Paracellular migration involves the release of endothelial-expressed vascular endothelial-cadherin (VE-cadherin) and is facilitated by intracellular membrane compartments containing a pool of platelet/endothelial-cell adhesion molecule 1 (PECAM1) and possibly other endothelial-cell junctional proteins, such as junctional adhesion molecule A (JAM-A). Other molecules involved in paracellular transmigration are endothelial cell-selective adhesion molecule (ESAM), ICAM2 and CD99. c | Transcellular migration occurs in “thin” parts of the endothelium, and therefore there is a distance for a leukocyte to migrate. ICAM1 ligation leads to translocation of ICAM1 to actin- and caveolae-rich regions. ICAM1-containing caveolar link together forming vesiculo-vacuolar organelles (VVOs) that form an intracellular channel through which a leukocyte can migrate. Ezrin, radixin and moesin (ERM) proteins could act as linkers between ICAM1 and cytoskeletal proteins (such as actin and vimentin), causing their localization around the channel, thereby providing structural support for the cell under these conditions. d | Migration through the endothelial basement membrane and pericyte sheath can occur through gaps between adjacent pericytes and regions of low protein deposition within the extracellular matrix. This response can be facilitated by αβ-integrin and possibly proteins, such as matrix metalloproteinases (MMPs) and neutrophil elastase (NE). ERM, ezrin, radixin and moesin, LFA1, lymphocyte function-associating antigen 1.
How do the leukocytes move within the tissue?
Leukocytes use amoeboid cell migration mechanisms

- Amoeboid migration is very different from mesenchymal or collective migration modes employed by other cell types.

- Amoeboid migration is fast (up to 30 μm/min), lacks strong adhesive interactions to the tissue and commonly preserves tissue integrity rather than degrading it.

- Four steps mediate the amoeboid migration cycle.
**4-step mechanisms of amoeboid migration**

1. The leading edge protrudes one or several **pseudopods** by actin flow,
2. protruding membrane and surface receptors interact with the substrate,
3. actomyosin-mediated contraction of the cell body occurs in mid-region, and
4. so the rear of the cell moves forward.

- These steps occur in a cyclic manner, generating forward movement:

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**Diagram notes:**

- A: Immobile
  - Lack of receptor polarization

- B: Polarization, random migration
  - Uropod
  - Mid-body
  - Leading edge
  - ICAM-1, -3
  - CD44
  - CD43
  - $\beta_1$ integrins
  - ERM
  - GMI-1
  - Microdomains
  - Mitochondria

- C: Filamentous actin
  - LFA-1 (intermediate-affinity)
  - Chemokine sensitivity
  - TCR sensitivity

- D: PIP$_3$
  - ROCK
  - CTEN
  - DOCK2

- E: Microtubules
  - MMP2
  - MMP9
  - Fragment

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**Mechanisms (4 steps):**

1. **Leading edge** protrudes one or several **pseudopods** by actin flow,
2. **Protruding membrane and surface receptors** interact with the substrate,
3. **Actomyosin-mediated contraction** of the cell body occurs in mid-region, and
4. **So the rear of the cell moves forward.**
Cell trafficking in immunology
interstitial leukocyte migration

Leading edge:
high density of GPCR-receptors:

- fMLP (N-formyl-Met-Leu-Phe) receptor and
- C5a receptor
- chemokine receptors including CCR7, CXCR4, CXCR5, CCR3
- The leukotriene B4 receptor BLT1
- sphingosine-1-phosphate receptors
- lysophosphatidic acid (LPA) receptors

GPCR-signaling: results in local activation of Rac

- Rac induces actin polymerization through WAVE (Scar) and Arp2/3. WAVE, a member of the WASP family of actin-binding proteins, mediates actin filament formation. Arp2/3 causes sideward branching of actin filaments. Together, these activities generate interconnected, branched networks.
Cell trafficking in immunology
interstitial leukocyte migration

**Mid-body:**
- generates actomyosin-based stiffness and contractility
- limits lateral protrusions and thereby maintains a stable, bipolar cortex
- The cytoskeletal motor protein myosin II located in the central and rear regions of leukocytes promotes actin filament contraction and limits lateral protrusions
- Myosin II cross-links actin filaments in parallel, forming the contractile shell required to hold the extending cell together and propelling the cell nucleus, the most rigid part of the cell, forward

**signaling key player:** Rho and ROCK
Upstream of myosin II (unclear mechanisms) PI(3)K-γ and possibly DOCK-2 suppress lateral protrusions
The phosphatase PTEN also contributes to lateral stability by preventing ectopic protrusion formation. PTEN is excluded from the leading edge but active in lateral and rear cell parts, where it dephosphorylates kinases, including PI(3)K and Akt, as well as phosphatidylinositol-(3,4,5)-trisphosphate, and thereby counteracts protrusion formation
Cell trafficking in immunology
interstitial leukocyte migration

Uropod=trailing edge:
- contains the highly glycosylated surface receptors CD43 and CD44, adhesion receptors including intercellular adhesion molecule (ICAM)-1, ICAM-3, \( \beta 1 \) integrins and ERM adaptor proteins
- The uropod mediates cell–matrix and cell–cell interactions during migration (putative anchoring function)
- Contains rearward-polarized microtubules, the Golgi, and abundant actin-binding ERM (ezrin, radixin, moesin) proteins
- In association with microtubules, mitochondria localize to the rear of the cell, which, presumably owing to local ATP delivery to the region of ATP-dependent actomyosin contraction, is required for proper polarization, uropod retraction and migration
Cell motility relies on the remodeling of the cell shape:

How are the external motility signals integrated to coordinate cell shape remodeling?
The initial response of a cell to a migration-promoting agent is to **polarize** and **extend protrusions** in the direction of migration. These protrusions can be large, **broad lamellipodia or spike-like filopodia**, are usually driven by **actin polymerization**, and are stabilized by adhering to the extracellular matrix (ECM) or adjacent cells via transmembrane receptors linked to the actin cytoskeleton. These adhesions serve as traction sites for migration as the cell moves forward over them, and they are disassembled at the cell rear, allowing it to detach.

**Cell Migration: Integrating Signals from Front to Back**
Anne J. Ridley, Martin A. Schwartz, Keith Burridge, Richard A. Firtel, Mark H. Ginsberg, Gary Borisy, J. Thomas Parsons and Alan Rick Horwitz (December 4, 2003)
Actin cytoskeleton organization at the two poles of a migrating T cell. Schematic representations of the ultrastructure of the actin cytoskeleton networks at the leading and trailing edges of the migrating T cell. At the leading edge, the T cell that migrates on a 2D surface emits a protrusion that alternates between a lamellipodium and a pseudopodium. It contains a very dynamical and highly branched actin meshwork. At the trailing edge, the T cell uropod is made of a network of parallel actin bundles that can slide along each other to generate contractile forces.
ATP-bound actin is added to the fast growing barbed end of filaments via the combined action of profilin, which prevents self-nucleation of actin monomers and actin-nucleating proteins (formin FMLN1 or WASP-family proteins) both of which are under the control of RhoGTPases.

Depolymerization is promoted by cofillin, which stimulates dissociation of ADP-bound actin at the pointed end of filaments. The rate of cofillin-mediated depolymerization can be controlled by Rho via Rock.
In addition to be elongated by formins, actin filaments can build networks in multiple ways. Actin bundles or cables with parallel or anti-parallel orientation of actin filaments are assembled by cross-linking proteins such as fimbrin. Actin filaments can also be cross-linked in a non-parallel fashion via filamin to create a gelled network.

Branched networks are promoted by the Arp2/3 complex that initiates nucleation of branched filaments on the side of existing ones. This activity is driven by WASP-family proteins and stabilized by HS-1. An additional important regulation of actin cytoskeleton networks is mediated by capping proteins such as gelsolin, which bind the plus end of actin filaments to prevent monomer exchange.
Cytoskeletal rearrangements
Basic Regulation of Actin Assembly

- Actin filaments not only generate forces while they elongate. They also generate the cell contractile forces via the intercalation of the molecular motor myosin between parallel actin filaments, which results in filament sliding.
- Such process is regulated by the control of the myosin light chain phosphatase and kinase activities, as well as by the degree of actin cross-linking via α-actinin.
Basics of Actin Assembly

Actin Filament Elongation, Branching and Stabilization
Actin Filament Crosslinking and Myosin-Driven Contraction
# Cytoskeletal rearrangements

## Actin

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Function</th>
<th>Associated immune-related disease</th>
<th>Reference</th>
</tr>
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<tr>
<td>a-actin</td>
<td>ACTN1</td>
<td>Actin crosslinking</td>
<td>ACTN1-related thrombocytopenia</td>
<td>(54, 55)</td>
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<td>Arp2</td>
<td>ACTR2</td>
<td>Actin branching</td>
<td>n.r.</td>
<td>(2, 54)</td>
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<td>n.r.</td>
<td>(2, 54)</td>
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<td>Cofilin</td>
<td>CTSZ</td>
<td>Limb detachment</td>
<td>n.r.</td>
<td>(56-57)</td>
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<td>Cdc42</td>
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<td>Filopodia assembly</td>
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<td>(58)</td>
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<td>GTP4</td>
<td>TIP4P10</td>
<td>Membrane curvature, WASP activation</td>
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<td>(59-61)</td>
</tr>
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<td>Collin</td>
<td>CFL1</td>
<td>Filament disassembly</td>
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<td>(62)</td>
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<td>Corrin1A</td>
<td>CORO1A</td>
<td>Arp 2/3 inhibition</td>
<td>Moderate to severe combined immunodeficiency</td>
<td>(53-55)</td>
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<td>Dock2</td>
<td>DOCK2</td>
<td>Rac1 activation</td>
<td>Primary immunodeficiency with early-onset invasive infections</td>
<td>(56, 57)</td>
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<td>Dock8</td>
<td>DOCK8</td>
<td>Cdc42 and Rac1 activation</td>
<td>Primary immunodeficiency with impaired cellular and humoral immunity</td>
<td>(58-70)</td>
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<td>Drehin</td>
<td>DNM1</td>
<td>Actin bundling, microtubule interaction</td>
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<td>(71-73)</td>
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<td>Ezrin</td>
<td>EZR</td>
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<td>(74-76)</td>
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<td>Filamin</td>
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<td>(77-79)</td>
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<td>Formin-like 1</td>
<td>FMNL1</td>
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<td>n.r.</td>
<td>(80)</td>
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<td>Gelsolin</td>
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<td>(81)</td>
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<td>(85)</td>
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<td>Autosomal recessive leukocyte adhesion deficiency syndrome-III (LAD-III)</td>
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<td>STK4</td>
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<td>T cell immunodeficiency</td>
<td>(51-53)</td>
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<td>RhoC</td>
<td>ROCK1</td>
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<td>SRFAP2</td>
<td>Membrane curvature, mDia1 inhibition</td>
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<td>Talin</td>
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<td>WIP</td>
<td>WIP1</td>
<td>WASP activation</td>
<td>Primary immunodeficiency resembling the Wiskott–Aldrich syndrome</td>
<td>(122-124)</td>
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</tbody>
</table>

n.r., not reported.

*For a list of the many genes encoding the various PI3K subunits and isoforms, see Ref. (103).*
1. actin-integrin interplay: no direct interaction! To exert traction forces
2. actin-motility receptors interplay: chemokine receptors: promoting adhesion
3. actin-antigen receptor (TCR) interplay:
   stop signal in order to assemble the immunological synapse
How do the cells know that and where they have to migrate?

Signals that induce and coordinate movement: Chemokines
Chemokines

**Definition:**
Chemokines are chemotactic cytokines that control the migratory patterns and positioning of immune cells. Chemokine function is critical for all immune cell movement ranging from the migration required for immune cell development and homeostasis, to that required for the generation of primary and amnestic cellular and humoral immune responses, to the pathologic recruitment of immune cells in disease. Chemokines are a group of small (∼8–14 kDa), mostly basic, structurally related molecules that regulate cell trafficking of various types of leukocytes through interactions with a subset of seven-transmembrane, G protein–coupled receptors. About 40 chemokines have now been identified in humans. They mainly act on neutrophils, monocytes, lymphocytes, and eosinophils and play a pivotal role in host defense mechanisms.

**Chemokine classes**
- **CC**
- **CXC**
- **C**
- **CX$_3$C**
Chemokines: A New Classification System and Their Role in Immunity

The last Keystone Chemokine Symposium. Chemokines have been divided into the two major subfamilies on the basis of the arrangement of the two N-terminal cysteine residues, CXC and CC, depending on whether the first two cysteine residues have an amino acid between them (CXC) or are adjacent (CC). The genes for these families are currently designated SCY (small secreted cytokine) with SCYa corresponding to the CC subfamily and SCYb to the CXC subfamily. Two other classes of chemokines have been described: lymphotactin (C or SCYc) and fractalkine (CX3C or SCYd). The former one lacks cysteines one and three of the typical chemokine structure (Kelner et al., 1994), while the latter one exhibits three amino acids between the first two cysteines and is also the only membrane-bound chemokine through a mucin-like stalk (Bazan et al., 1997). The proposed chemokine nomenclature is based on the chemokine receptor nomenclature currently in use, which uses CC, CXC, XC, or CX3C followed by R (for receptor) and then a number.
CCL19 and CCL21:
- both binding to CCR7
- guiding DCs and T-cells
- CCL19: internalization of receptor
CCL19/CCL21: chemokine signaling via CCR7
Homing of T-cells and guidance of DCs to lymph nodes

CCL19>> internalization of the receptor

Bardi, G., Lipp, M., Baggilini, M. & Loetscher, P.
The T cell chemokine receptor CCR7 is internalized on stimulation with ELC, but not with SLC. *Eur. J. Immunol.* 31, 3291–3297 (2001)
Which diseases originate/are associated from/with defective migration?

impact of proper cellular locomotion
<table>
<thead>
<tr>
<th>Disease</th>
<th>Key effector cell</th>
<th>Proposed leukocyte receptors for endothelial traffic signals</th>
<th>GPCR</th>
<th>Integrin*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute inflammation</strong></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td>Neutrophil</td>
<td>PSGL-1</td>
<td>CXCR1, CXCR2, PAFR, BLT1</td>
<td>LFA-1, Mac-1</td>
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<td>Stroke</td>
<td>Neutrophil</td>
<td>L-selectin, PSGL-1</td>
<td>CXCR1, CXCR2, PAFR, BLT1</td>
<td>LFA-1, Mac-1</td>
</tr>
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<td>Ischemia-reperfusion</td>
<td>Neutrophil</td>
<td>PSGL-1</td>
<td>CXCR1, CXCR2, PAFR, BLT1</td>
<td>LFA-1, Mac-1</td>
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<td><em>T</em>1</td>
<td>Monocyte</td>
<td>PSGL-1</td>
<td>CCR1, CCR2, BLT1, CXCR2, CCR3</td>
<td>VLA-4</td>
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<td>Rheumatoid arthritis</td>
<td>Monocyte</td>
<td>PSGL-1</td>
<td>CCR3, CCR6</td>
<td>VLA-4, LFA-1</td>
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<tr>
<td><em>T</em>1</td>
<td>Neutrophil</td>
<td>L-selectin, PSGL-1</td>
<td>CCR2, CCR6</td>
<td>VLA-1, VLA-2, VLA-4, LFA-1</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Skin-homing <em>T</em>1</td>
<td>CLA</td>
<td>CCR4, CCR10, CXCR3</td>
<td>VLA-4, LFA-1</td>
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<tr>
<td>Crohn disease</td>
<td>Gut-homing <em>T</em>1</td>
<td>PSGL-1</td>
<td>CCR9, CCR3</td>
<td>α9β2, LFA-1</td>
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<tr>
<td>Type I diabetes</td>
<td><em>T</em>1</td>
<td>PSGL-1</td>
<td>CCR4, CCR5</td>
<td>VLA-4, LFA-1</td>
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<tr>
<td>Allograft rejection</td>
<td>CD8</td>
<td>L-selectin (?, PSGL-1)</td>
<td>CCR3</td>
<td>VLA-4, LFA-1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>CD8</td>
<td>PSGL-1</td>
<td>CCR3, CCR5, CXCR6</td>
<td>VLA-4</td>
</tr>
<tr>
<td>Lupus</td>
<td><em>T</em>1</td>
<td>None</td>
<td>CCR3, ChemR23</td>
<td>LFA-1, Mac-1</td>
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<tr>
<td><em>T</em>2</td>
<td>Plasmacytoid DC</td>
<td>L-selectin, CLA</td>
<td>CCR7, CCR3</td>
<td>LFA-1</td>
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<tr>
<td>Asthma</td>
<td><em>T</em>2</td>
<td>PSGL-1</td>
<td>CCR4, CCR8, BLT1</td>
<td>LFA-1</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>PSGL-1</td>
<td>CCR3, PAFR, BLT1</td>
<td>VLA-4, LFA-1</td>
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<tr>
<td>Mast cells</td>
<td>PSGL-1</td>
<td>CCR2, CCR3, BLT1</td>
<td>VLA-4, LFA-1</td>
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<tr>
<td>Atopic dermatitis</td>
<td>Skin-homing <em>T</em>2</td>
<td>CLA</td>
<td>CCR4, CCR10</td>
<td>VLA-4, LFA-1</td>
</tr>
</tbody>
</table>

*Various β1 integrins have been linked in different ways in basal lamina and interstitial migration of distinct cell types and inflammatory settings. *In some settings, Mac-1 has been linked to transmigration. αCD44 can act in concert with VLA-4 in particular models of leukocyte arrest. * *T*2 cells require VAP-1 to traffic to inflamed liver.
<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Function</th>
<th>Associated immune-related disease</th>
<th>Reference</th>
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<tbody>
<tr>
<td>a-actinin</td>
<td>ACTN1</td>
<td>Actin crosslinking</td>
<td>ACTN1-related thrombocytopenia</td>
<td>(64, 56)</td>
</tr>
<tr>
<td>Arp2</td>
<td>ACTR2</td>
<td>Actin branching</td>
<td>n.r.</td>
<td>(2, 50)</td>
</tr>
<tr>
<td>Arp3</td>
<td>ACTR3</td>
<td>Actin branching</td>
<td>n.r.</td>
<td>(2, 50)</td>
</tr>
<tr>
<td>Cathepsin X</td>
<td>CTSZ</td>
<td>Uropod detachment</td>
<td>n.r.</td>
<td>(60, 57)</td>
</tr>
<tr>
<td>Cdc42</td>
<td>CDC42</td>
<td>Filopodia assembly</td>
<td>n.r.</td>
<td>(69)</td>
</tr>
<tr>
<td>CIP4</td>
<td>TRIP10</td>
<td>Membrane curvature, WASP activation</td>
<td>n.r.</td>
<td>(60–61)</td>
</tr>
<tr>
<td>Cofilin</td>
<td>CFL1</td>
<td>Filament disassembly</td>
<td>n.r.</td>
<td>(62)</td>
</tr>
<tr>
<td>Corin1A</td>
<td>CORO1A</td>
<td>Arp 2/3 inhibition</td>
<td>Moderate to severe combined immunodeficiency</td>
<td>(63–69)</td>
</tr>
<tr>
<td>DOCK2</td>
<td>DOCK2</td>
<td>Rac1 activation</td>
<td>Primary immunodeficiency with early-onset invasive infections</td>
<td>(65, 67)</td>
</tr>
<tr>
<td>DOCK8</td>
<td>DOCK8</td>
<td>Cdc42 and Rac1 activation</td>
<td>Primary immunodeficiency with impaired cellular and humoral immunity</td>
<td>(68–70)</td>
</tr>
<tr>
<td>Drebrin</td>
<td>DBN1</td>
<td>Actin bundling, microtubule interaction</td>
<td>n.r.</td>
<td>(71–73)</td>
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<td>Ezrin</td>
<td>EZR</td>
<td>Actin–transmembrane proteins crosslinking</td>
<td>n.r.</td>
<td>(74–76)</td>
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<td>Filamin A</td>
<td>FLNA</td>
<td>Actin crosslinking</td>
<td>n.r.</td>
<td>(77–79)</td>
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<td>Formin-like 1</td>
<td>FMNL1</td>
<td>Filament elongation</td>
<td>n.r.</td>
<td>(80)</td>
</tr>
<tr>
<td>Gelsolin</td>
<td>GSN</td>
<td>Filament capping</td>
<td>n.r.</td>
<td>(61)</td>
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<td>HS1</td>
<td>WHAAQ</td>
<td>Branching stabilization</td>
<td>n.r.</td>
<td>(82–84)</td>
</tr>
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<td>INF2</td>
<td>INF2</td>
<td>Filament elongation</td>
<td>n.r.</td>
<td>(80)</td>
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<tr>
<td>Kindlin3</td>
<td>FERM1</td>
<td>Actin-integrins interplay</td>
<td>Autosomal recessive leukocyte adhesion deficiency syndrome-III</td>
<td>(69)</td>
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<tr>
<td>L-plakin</td>
<td>LCP1</td>
<td>Actin bundling</td>
<td>n.r.</td>
<td>(41)</td>
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<tr>
<td>nDia1</td>
<td>DIAPH1</td>
<td>Filament elongation</td>
<td>n.r.</td>
<td>(67–69)</td>
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<tr>
<td>MLCK</td>
<td>MYLK</td>
<td>Actomyosin contraction</td>
<td>n.r.</td>
<td>(60)</td>
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<td>Moesin</td>
<td>MSN</td>
<td>Actin–transmembrane proteins crosslinking</td>
<td>n.r.</td>
<td>(70)</td>
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<tr>
<td>Mst1</td>
<td>STK4</td>
<td>Chemokine receptor-integrins interplay</td>
<td>T cell immunodeficiency</td>
<td>(91–93)</td>
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<tr>
<td>Myo1g</td>
<td>MYO1G</td>
<td>Actin contraction</td>
<td>n.r.</td>
<td>(17)</td>
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<td>Myo1A</td>
<td>MYH9</td>
<td>Actomyosin contraction</td>
<td>n.r.</td>
<td>(90, 94–96)</td>
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<td>Paxillin</td>
<td>PXN</td>
<td>Actin-integrins interplay</td>
<td>n.r.</td>
<td>(99–101)</td>
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<td>PI3K</td>
<td>PIK3</td>
<td>PI3,4,5-P3 generation</td>
<td>n.r.</td>
<td>(66, 102, 103)</td>
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<td>Profilin</td>
<td>PNF2</td>
<td>Actin polymerization</td>
<td>n.r.</td>
<td>(104, 105)</td>
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<tr>
<td>Rac1</td>
<td>RAC1</td>
<td>Actin branching (forminoids)</td>
<td>n.r.</td>
<td>(69)</td>
</tr>
<tr>
<td>Rap1</td>
<td>RAP1A</td>
<td>Chemokine receptor-integrins interplay</td>
<td>n.r.</td>
<td>(106–110)</td>
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<td>RapL</td>
<td>RASSF5</td>
<td>Chemokine receptor-integrins interplay</td>
<td>n.r.</td>
<td>(91, 108)</td>
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<td>RhoA</td>
<td>RHOA</td>
<td>Actomyosin contraction</td>
<td>n.r.</td>
<td>(111)</td>
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<tr>
<td>Rock</td>
<td>ROCK1</td>
<td>Actomyosin contraction</td>
<td>n.r.</td>
<td>(69)</td>
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<tr>
<td>Sharpin</td>
<td>SHARPIN</td>
<td>Actin-integrins interplay</td>
<td>n.r.</td>
<td>(112)</td>
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<td>srcGAP2</td>
<td>SRGAP2</td>
<td>Membrane curvature, mDia1 inhibition</td>
<td>n.r.</td>
<td>(113)</td>
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<td>Talin</td>
<td>TLN1</td>
<td>Actin-integrins interplay</td>
<td>n.r.</td>
<td>(114)</td>
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<td>Vinculin</td>
<td>VCL</td>
<td>Actin-integrins interplay</td>
<td>n.r.</td>
<td>(115)</td>
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<td>WASH</td>
<td>WASH1</td>
<td>Arp 2/3 activation</td>
<td>n.r.</td>
<td>(118)</td>
</tr>
<tr>
<td><strong>WASP</strong></td>
<td><strong>WAS</strong></td>
<td><strong>Arp 2/3 activation</strong></td>
<td><strong>Wiskott-Aldrich syndrome</strong></td>
<td><strong>(53, 117–119)</strong></td>
</tr>
<tr>
<td>WAVE2</td>
<td>WASF2</td>
<td>Arp 2/3 activation</td>
<td>n.r.</td>
<td>(115, 120, 121)</td>
</tr>
<tr>
<td>WIP</td>
<td>WIPFI</td>
<td>WASP activation</td>
<td>Primary immunodeficiency resembling the Wiskott–Aldrich syndrome</td>
<td>(122–124)</td>
</tr>
</tbody>
</table>

n.r., not reported.

For a list of the many genes encoding the various PI3K subunits and isoforms, see Ref. (102).
Loss of WASP (Wiskott–Aldrich syndrome protein) activity leads to Wiskott–Aldrich syndrome, an X-linked disease that is associated with defects in a broad range of cellular processes, resulting in **complex immunodeficiency, autoimmunity and microthrombocytopenia**.

Fig. 2. Lack of WASp causes defective function of multiple haematopoietic cell lineages. WASp is required for many functions in haematopoietic cells and its absence results in defects of cellular function. The combination of defective function of multiple immune cell lineages culminates in global dysregulation of immune function, which manifests as abnormal inflammatory responses, autoimmunity and susceptibility to malignancy. In addition, lack of WASp causes a specific platelet defect, which results in increased platelet destruction and bleeding tendency.
Figure 3 | Wiskott–Aldrich syndrome protein function in immune cells. Wiskott–Aldrich syndrome protein (WASP) is required for many functions in lymphoid and myeloid immune cells. Many of these, such as phagocytosis and podosome assembly, relate to the role of WASP in regulating the polymerization of new branched actin filaments. Other functions of WASP depend on its activity as a scaffold protein for assembly of effective signalling complexes downstream of antigen receptor or integrin engagement. BCR, B cell receptor; NK, natural killer; TCR, T cell receptor.
Summary

- Trafficking of leukocytes is central to immune cell development, immunosurveillance and effector function.
- Innate and adaptive immune functions depend upon interstitial leukocyte migration.
- Inflammation: Activation of endothelial cells by pro-inflammatory cytokines from resident immune cells.
- To enter tissues, leukocytes pass endothelial barrier (multistep cascade) in a selectin and integrin-dependent manner.
- Within the tissue, leukocytes migrate in an amoeboid fashion (4 steps) which differs from mesenchymal migration.
- Polarization of cells > cellular shape remodeling: leading edge; mid-body; uropod.
- Cytoskeletal rearrangement: signaling that regulates actin assembly/disassembly.
- Soluble factors that initiate migration/maturation: Chemokines.
- CCL19/CCL21 as an example for guiding DCs and T-cells to and within lymphnodes.
- The Wiskott–Aldrich syndrome: defective WASP results in complex immunodeficiency.