Mechanisms and *in vivo* functions of contact inhibition of locomotion

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Abstract | Contact inhibition of locomotion (CIL) is a process whereby a cell ceases motility or changes its trajectory upon collision with another cell. CIL was initially characterized more than half a century ago and became a widely studied model system to understand how cells migrate and dynamically interact. Although CIL fell from interest for several decades, the scientific community has recently rediscovered this process. We are now beginning to understand the precise steps of this complex behaviour and to elucidate its regulatory components, including receptors, polarity proteins and cytoskeletal elements. Furthermore, this process is no longer just *in vitro* phenomenology; we now know from several different *in vivo* models that CIL is essential for embryogenesis and in governing behaviours such as cell dispersion, boundary formation and collective cell migration. In addition, changes in CIL responses have been associated with other physiological processes, such as cancer cell dissemination during metastasis.

The term "contact inhibition" was first coined by the pioneering cell biologist Michael Abercrombie in 1954 (REF. 1). The discovery that numerous cell types undergo a "directional prohibition of movement" upon migratory collision was ground-breaking, not because the process was realized to be crucial for animal physiology, but because of its ability to provide a framework to investigate the general mechanisms behind cell motility. Abercrombie spent his career studying contact inhibition of locomotion (CIL) and in doing so elucidated a number of fundamental aspects of cell migration, which forms the basis with regards to how the community thinks about the motility process to this day[2].

As will become clear in this Review, the process of CIL is multifaceted. Understanding CIL requires both an understanding of cell migration and how cells interact and dynamically modulate their polarity; indeed, such aspects need to be considered for almost all cell biological phenomena. However, CIL fell from interest for a number of decades after Abercrombie's death in 1979, and this reduced interest was due to several reasons[3]. First, the initial work on CIL stretched the boundaries of their understanding of cell motility at that time; for example, cellular actin was only directly visualized for the first time in 1978 (REF. 4). Second, the function of CIL, if any, in animal physiology was totally unknown. These problems in understanding CIL are now being overcome. The field of cell motility has matured, and our knowledge of the molecular mechanisms of cell migration is far greater than in Abercrombie's time. Furthermore, live imaging of cellular behaviours *in vivo* is now commonplace. We are therefore armed with a far better knowledge base to elucidate the mechanisms of CIL and its functions in processes such as animal development.

In this Review, we outline our current understanding of the process of CIL and describe the quantitative assays available to measure this phenomenon. We discuss the mechanisms involved in CIL behaviours and how these mechanisms mediate distinct steps of the CIL response. Finally, we highlight the recently discovered functions of CIL in animal development and discuss as yet unexplored roles for this process during different physiological processes.

Types of CIL behaviour

Precisely what does it mean for a cell to undergo CIL? Let us begin with what CIL is not. Although the term 'contact inhibition' initially referred to effects on cell locomotion, the phrase was adopted in the 1960s by those studying contact inhibition of proliferation, a process in which cell division is inhibited as cell density increases. This adoption led to confusion that persists to this day despite warnings from Michael Stoker, a pioneer of contact inhibition of proliferation research. In fact, Stoker preferred the term "density dependent inhibition of growth" for the process that he studied because there was evidence to indicate that physical contact was not needed to inhibit proliferation[5–7]. Moreover, Stoker suggested that the term 'contact inhibition' should be restricted to describing the arrest of movement as defined by Abercrombie and Heaysman[8]. So far, there

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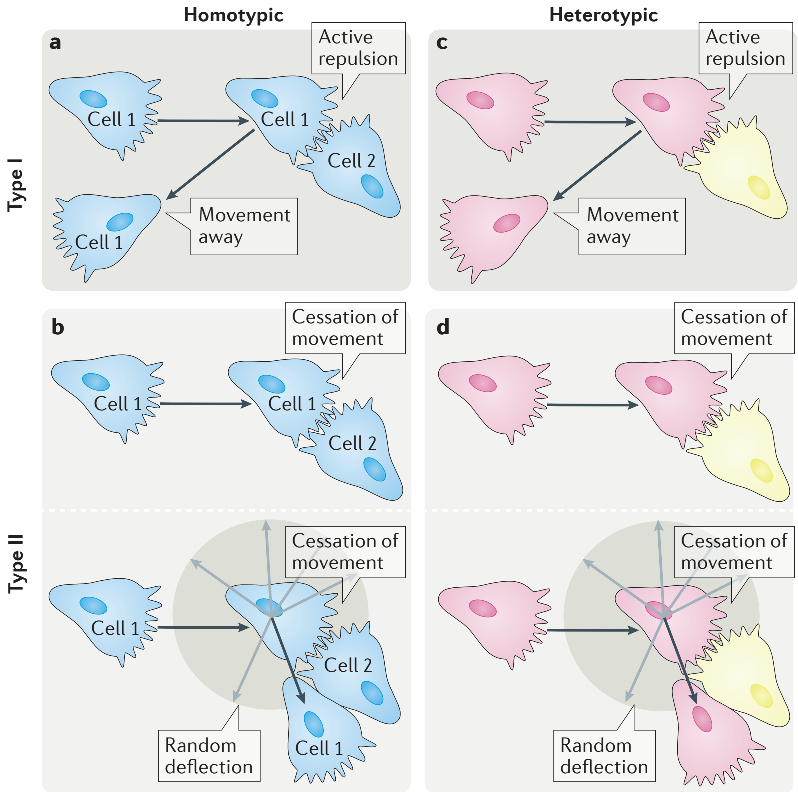


Figure 1 | **Types of contact inhibition of locomotion behaviours and their outcomes.** **a**,**b** | Homotypic contact inhibition of locomotion (CIL) interactions, which involve collisions between cells of the same type (cells 1 and 2). Collisions involving type I CIL involve active cellular retraction resulting in a predominant movement away from the colliding partner (**a**). By contrast, collisions involving type II CIL will lead to cells simply ceasing movement upon contact with another cell or being randomly deflected around the collision (**b**). **c**,**d** | Heterotypic CIL interactions, which involve collisions between different cell types can also result in type I (part **c**) or type II (part **d**) responses.

is no clear mechanistic connection between CIL and contact inhibition of proliferation, and they should not be thought of as interrelated processes as some people have suggested[9].

Definition of CIL. So, confusion sorted. Not quite. Even Abercrombie's definition of CIL changed over his career as he and colleagues struggled to define its essence. The variability in the definitions of CIL used in current publications suggests that the community is revisiting these exact same problems. Thus, a discussion of the history is worthwhile or else we risk repeating the lack of clarity. In Abercrombie's final paper, he defined CIL as "the phenomenon of a cell ceasing to continue moving in the same direction after contact with another cell" (REF. 10). By contrast, a complete loss of CIL, according to Abercrombie's definition, involves the "continued movement such as would carry one cell over the surface of another" (REF. 11). Note that this definition is purposefully vague with regards to what happens after contact. Does the cell simply stop moving? Does it repolarize and migrate away? Is it randomly deflected from the colliding cell? Any of these behaviours constitute CIL by this simple definition. Other researchers of CIL noted with obvious consternation that "quite a number of phenomena having to do with cells' influences upon one another's movements have come to be regarded as expressions of contact inhibition. However, no single, central mechanism has been shown to underlie them all" (REF. 12). Even a cessation of leading edge dynamics upon collision, which is often assumed to be a hallmark of CIL, was realized to be a poor predictor of contact inhibition[12–15]. Indeed, Abercrombie even stated that leading edge paralysis was a "red herring" with regards to the underlying mechanism of CIL[14].

Leading edge
This term is used synonymously with lamellae here and describes the front of a migrating cell that contains an actin network that pushes out the plasma membrane, which is involved in generating the forces underlying cell migration.

Variability in CIL responses. Efforts made to clarify CIL behaviours included classifying CIL into specific types, with some envisioning up to six different CIL responses[12]. By contrast, Abercrombie simplified CIL into two types. The first type (type I) involved the local paralysis and contraction of the leading edge, with contraction being the defining response[15,16]. The second type (type II) involved the difficulty for a cell to move across the surface of another cell because it may simply be less adhesive than the substratum[16,17]. Taking this classification a step further to consider the final outcome of the response, type I CIL would lead to an active movement away from the colliding partner (FIG. 1a; Supplementary information S1,S2 (movies)), whereas type II CIL would result in a simple cessation of movement or a random deflection (FIG. 1b; Supplementary information S3 (movie)). It is possible that type II CIL is a more passive response and is controlled by the mechanics of the collision. Indeed, membrane tension and external forces affect the actin polymerization machinery at the leading edge, which can alter migratory behaviour[18–20]. By contrast, type I CIL must involve active repolarization signals and is probably also controlled by specific surface receptors that permit cell–cell recognition, which may not be required for type II behaviour.

Regardless of the outcome, it is important to stress that CIL does not constitute a single behaviour, which makes its description and quantification highly complex (BOX 1). Even within a homogeneous population of cells, one may see a range of collision outcomes, which may be due to the variability of the response or the differences in the orientation of the colliding partners[11,14,21–23]. CIL is therefore not a binary behaviour; changing the geometry of the collision (for example, lamellae-to-lamellae versus lamellae-to-rear) or altering the signals involved in the interaction (such as a change in the expression of surface receptors) may lead to an entirely different type of CIL response. A complete failure in CIL (resulting in cells crawling on top of or beneath one another) has only been observed in a few cell types, with most involving interactions between cancer cells and normal cells[11] (Supplementary information S4 (movie)).

Another parameter that can modify CIL behaviour involves heterotypic versus homotypic interactions between colliding partners (FIG. 1c,d). There are many examples in which collisions between cells of the same type (homotypic CIL) yield completely different outcomes compared with collisions with other cells (heterotypic CIL). In some cases, one of the cells in a heterotypic collision may be completely defective in CIL and use the other as a substrate for its motility. In other cases, a heterotypic response may simply be subtly changed compared with the homotypic response, yielding only a slightly different type of CIL behaviour. Importantly, the ability of heterotypic collisions to produce non-mutual outcomes confers an added level of instructive power to the CIL process that can lead to emergent cellular behaviours during animal development (see the section 'Embryological functions of CIL' below).

Stages of the CIL response

Before we can elucidate the mechanisms controlling CIL, it is important to understand the possible regulatory stages of the process. For the purpose of this Review, we divide the response into four stages, which have some basis from experimentation. This division is somewhat arbitrary because these steps temporally overlap. Furthermore, it is important to note that not all cells undergoing CIL will experience all of these behaviours. For example, the final

Box 1 | Contact inhibition of locomotion assays

The variability in CIL behaviours makes it essential to choose the correct assay, with multiple assays typically required to fully describe the phenomenon. The currently available approaches for assaying CIL include:

Mixing assay

Two differentially labelled tissue explants are placed in culture at a short distance between each other, and the overlapping region resulting from the migratory outgrowth of both explants is quantified. When CIL responses are strong, cell migration from the explants ceases when one explant touches the other, whereas when CIL is impaired, an increase in overlap is observed[25,27,31,49] (see the figure, part **a**). A variant of this assay is to quantify the overlapping of individual cell protrusions under higher magnification, allowing for more detailed analysis of cell behaviour[27,48]. It is also possible to quantify the overlap between cell nuclei[1]; however, decreasing the strength of CIL does not always lead to nuclear overlap, making this assay less sensitive to subtle effects.

Radial outgrowth

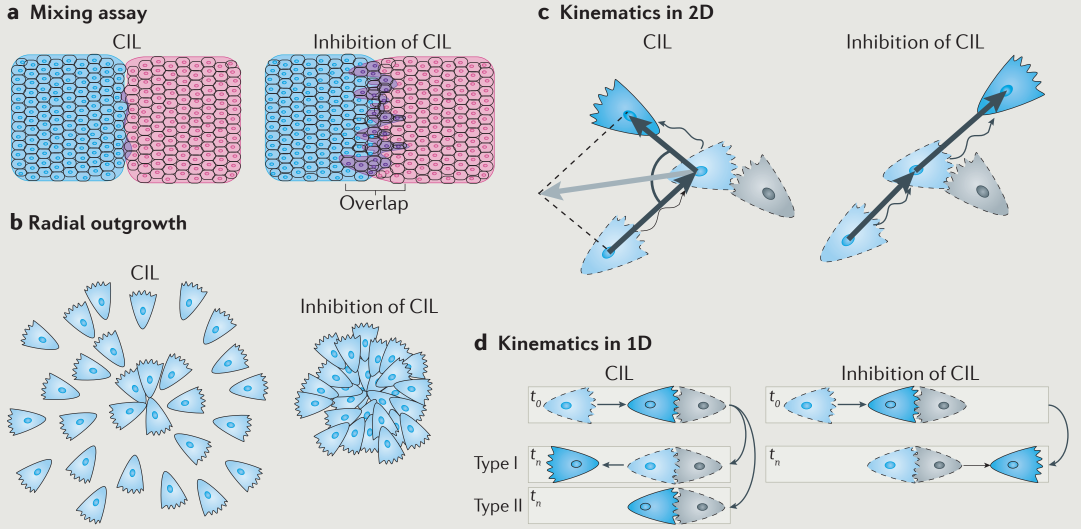
Explants of cells undergoing CIL radially disperse because this behaviour is the most efficient way for cells to spread (see the figure, part **b**). Cell dispersion can be quantified by measuring the distance between neighbouring cells upon explant outgrowth, as this distance increases in cells with strong CIL behaviour[27].

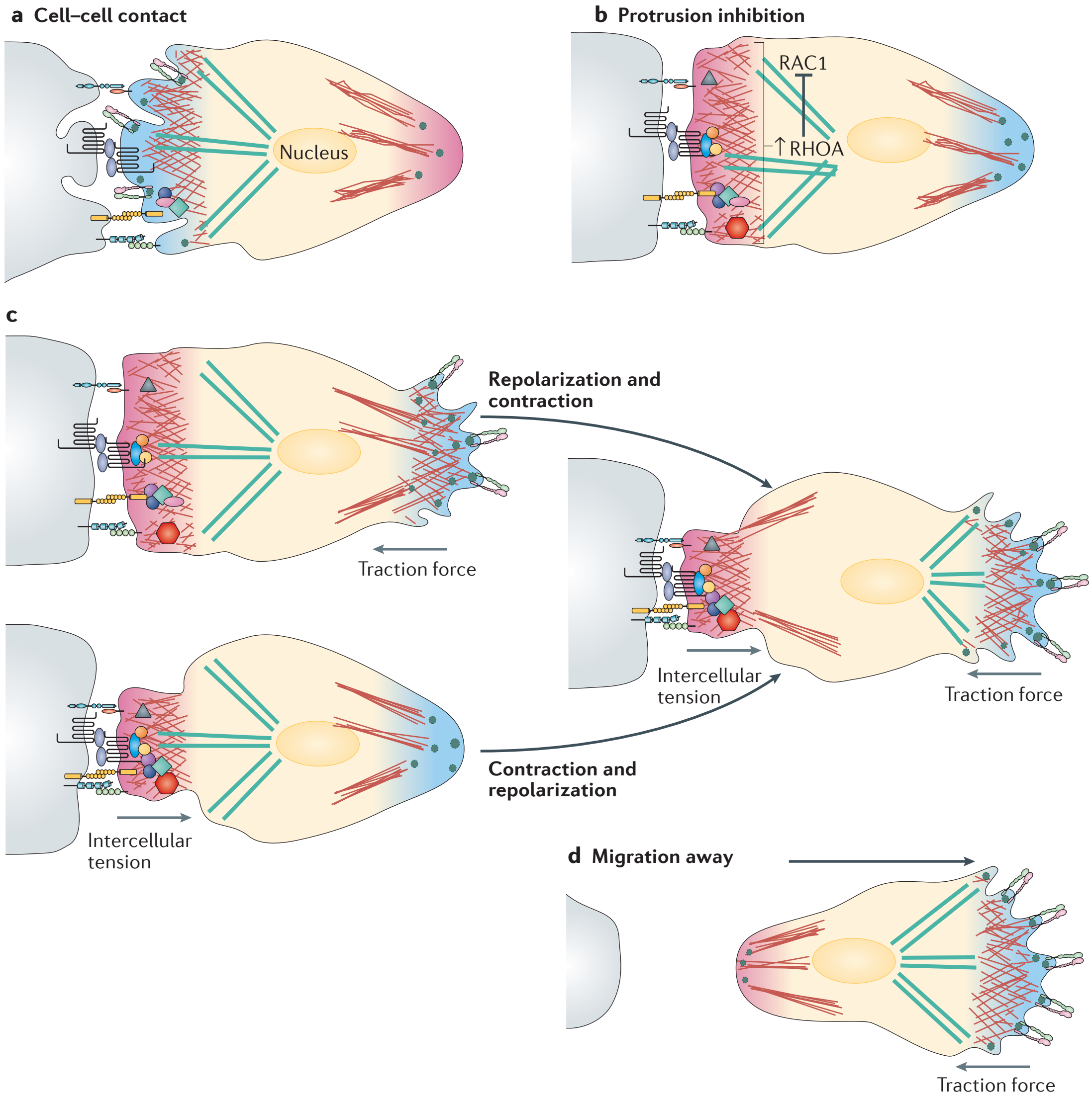
Kinematics in 2D

Cells are cultured on a 2D substrate (or examined *in vivo* if 2D descriptions are relevant) and imaged by time-lapse imaging. During CIL, cells alter their motion, which results in changes in velocity and acceleration (see the figure, part **c**). Note that velocity and acceleration are vectors and therefore measure changes in both speed and direction. Care must be taken to compare these motions with the motion of freely moving cells to distinguish CIL-specific effects. As collisions occur in many orientations, it is also important to meaningfully pool data (for example, normalize to movement at the time of collision) otherwise one will observe a random collection of vectors. This assay is a powerful way to describe many aspects of the motion changes surrounding collisions[25,26,59,98].

Kinematics in 1D

Cells are cultured on micropatterned stripes of extracellular matrix, and their migration is recorded (see the figure, part **d**). Compared with 2D kinematics, this approach increases the chance of collisions while limiting the degrees of freedom of motion, which eases interpretation. However, care must be taken to choose an optimal width of the micropattern because migration can be greatly affected by this parameter[99]. There are a number of possible outcomes of collisions in 1D, which depend on the type and the capacity of CIL response, including the following: repolarization and migration of the two cells away from each other; a non-mutual response with only one cell repolarizing; cells remain in contact; or cells migrate past or over each other[23,73,100]. In the figure part d t_0 denotes time before collision. t_n denotes time after collision.





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Component	Cell type
Cell–cell adhesion	
Cadherin	Neural crest cells[27,30,31], fibroblasts[33,35], epithelial cells[32,35] and myoblasts[34]
Additional, undefined adhesion complexes	*Drosophila melanogaster* macrophages[26] and fibroblasts[28,29]
Adhesion regulator	
α-Catenin and β-catenin	Epithelial cells[32], fibroblasts[36] and neural crest cells[27]
p120	Neural crest[27] and pancreatic carcinoma cells[38]
Cell–matrix adhesion	
Integrin	*D. melanogaster* macrophages[61] and myoblasts[34]
Focal adhesion remodelling	Neural crest cells[27,63]
Cytoskeletal components and their regulators	
Actomyosin contraction	Fibroblasts[54] and *D. melanogaster* macrophages[26]
Microtubule remodelling	Neural crest cells[48], *D. melanogaster* macrophages[26,59,93] and fibroblasts[60]
Diaphanous	*D. melanogaster* macrophages[26]
Clasp	*D. melanogaster* macrophages[93]

Component	Cell type
Signalling receptors	
Eph–ephrin	Prostate cancer cells[41,42] and Cajal–Retzius cells[40]
Slit–Robo	Fibroblasts[50]
Frizzled–WNT11	Neural crest cells[25]
Polarity modulators	
PAR3	Neural crest cells[48]
DSH	Neural crest cells[25]
PCK	Neural crest cells[25]
STBM	Neural crest cells[25]
Small GTPases and their regulators	
RAC1, CDC42	Fibroblasts[51] and prostate cancer cells[41]
RHOA and ROCK	Prostate cancer cells[42], fibroblasts[51,54] and neural crest cells[25]
TRIO	Neural crest cells[48]
SRGAP2	Fibroblasts[50]
VAV2	Prostate cancer cells[42]
NM23-H1	Glia[53]

Adherens junction
A cadherin-mediated cell–cell junction that is normally thought to mediate stable adhesion between epithelial cells.

Neural crest cells
A transient, vertebrate-specific embryonic cell population originating from the neural ectoderm, which undergoes a number of developmental migratory behaviours before differentiating into diverse cell types, such as melanocytes, cartilage and glia.

Epithelial–mesenchymal transition
(EMT). A process by which epithelial cells lose epithelial characteristics, such as their polarity and cell–cell adhesions, and gain characteristics thought to be specific to mesenchymal cells, such as enhanced motility and invasiveness.

outcome of Abercrombie's type I CIL is cell contraction and separation, which is markedly different from the non-repolarizing type II response (as discussed above). Therefore, different CIL responses are likely to feature distinct stages. We focus on hypothetical steps of classical type I CIL, which Abercrombie thought to be the prototypical CIL behaviour[16]. However, it is possible that other CIL types simply represent an abbreviated response that involves only some of these stages (for example, a type II CIL missing the last step of cells migrating away from the collision), and this framework is useful for studying CIL regardless of the response type.

The proposed sequence of events implicated in CIL is outlined in FIG. 2 and includes the following steps: first, cell–cell contact; second, inhibition of cell protrusive activities at the site of contact; third, contraction of protrusions upon cell contact and generation of a new protrusion; and, fourth, migration away from the collision. The first step of cell–cell contact is essential for CIL and distinguishes this process from other repulsive processes that involve cell responses at a distance (for example, chemorepulsion). Here, it is important to differentiate between cell contacts established during head-to-head collisions (lamellae-to-lamellae) versus other orientations because, as mentioned above, the geometry of the collision can affect the CIL response[11,14,21–23]. This initial contact is followed by a variable degree of protrusion inhibition. In many cases it is possible to observe a cessation of protrusion activity immediately after contact[24,25]; however, as mentioned earlier, this is not necessarily correlated with CIL capacity. Subsequently, the cell will undergo leading edge contraction and cell repolarization, although the precise order of these two events possibly dependends on the type of CIL. Although in some cell types contraction of lamellae occurs prior to cell repolarization[1,26], others have observed the opposite[27]. The final step of a stereotypic CIL response is migration away from the collision, which is likely to involve a re-activation of the migratory machinery that may have been affected by the initial collision.

◀ Figure 2 | **Stages of contact inhibition of locomotion and their regulatory mechanisms.** Example of a typical type I contact inhibition of locomotion (CIL) response involving a lamellae-to-lamellae cell interaction, which results in active repolarization and a change in the direction of cell migration. **a** | The initial step in the response upon collision is the generation of a cell–cell contact involving a range of possible receptors (including Eph–ephrin and SLIT2–ROBO4 interactions) and classical cell adhesion molecules (in particular, adherens junction components: cadherins (such as N-cadherin), p120, α- and β-catenin). **b** | Subsequently, there may be a variable amount of protrusion inhibition driven by the alteration of signalling by small GTPases, in particular by the change in the activation of mutually antagonistic RHOA and RAC1 GTPases (activation of RHOA and inactivation of RAC1) at the contact site. At the same time that RAC1 is inhibited at the cell–cell contact site, it becomes activated away from the collision. This process is mediated by the modulation of activity of various GTPase regulators, including SLIT–ROBO Rho GTPase activating protein 2 (SRGAP2; a RAC1 inhibitor), guanine nucleotide exchange factor (an activator of RHOA) and guanine nucleotide exchange factor triple functional domain protein (TRIO; an activator of RAC1). Regulation of GTPases can be modulated by additional signals such as Eph–ephrin and SLIT2–ROBO4 interactions, as well as by various polarity proteins, including partition defective 3 homologue (PAR3; which negatively regulates TRIO, thereby contributing to RAC1 inactivation). The planar cell polarity pathway, involving WNT11-induced recruitment of Dishevelled (DSH), Strabismus (STBM) and Prickle 1 (PCK) to the WNT receptor Frizzled (which promotes activation of RHOA), also regulates GTPases. This change in small GTPase activity may directly affect protrusions by altering actin polymerization at the leading edge or indirectly by a build-up in lamellar tension. Furthermore, there may be additional reorganization of the cytoskeleton, such as a modification of microtubule dynamics or stability. **c** | The cells then begin to contract and repolarize (with the order of these events possibly cell-type dependent). These processes require further actomyosin contraction and/or build-up of tension at the contact site, promoting contraction and a possible reorganization of focal adhesions. This event redistributes traction forces, thereby contributing to repolarization. Upon repolarization, a new leading edge is established, which is promoted by robust RAC1 activity. **d** | Finally, the cell migrates away from the colliding partner. It should be clarified that these hypothetical stages will not be completely distinct but will temporally overlap to facilitate an integrated and seamless response. **e** | Summary of cellular components identified to function in CIL and the respective cell types in which their involvement was described. NM23-H1, nonmetastatic protein 23 (also known as nucleoside diphosphate kinase A).

Molecular mechanisms of CIL

Although CIL behaviours are diverse, we are beginning to gain a clearer picture of the basic molecular mechanisms underlying the various steps of this phenomenon. Here, we discuss key molecular players and recently elucidated mechanisms underlying the distinct stages of the CIL response (FIG. 2).

Establishing cell–cell contact. Although cell–cell adhesion evidently has an important role in CIL, the molecular nature of the adhesion is unclear in many cell types[26–29]. Recent evidence has revealed that the initial cell contact during CIL often involves the formation of a transient cadherin-mediated intercellular junction. Cadherins constitute a family of transmembrane glycoproteins that are normally associated with epithelial monolayers and facilitate calcium-dependent cell–cell adhesion (FIG. 2a). Different cadherins, such as E-cadherin, N-cadherin and cadherin 11 (REFS. 27,30–35), are found at the cell–cell contact point during CIL in a range of cell types. Furthermore, numerous proteins involved in the formation of a stable adherens junction are also involved in CIL; such proteins include β-catenin, p120, vinculin and α-catenin[27,32,36]. It is not completely clear why these adherens junctions are transient during CIL, while having almost the same composition as a stable junction between epithelial cells. Recent work using Xenopus and zebrafish neural crest cells has shed some light on this problem by comparing junctional formation during responses that involve either a stable or transient adhesion. Cells specifically expressing E-cadherin remain in contact, whereas cells expressing N-cadherin undergo repulsion[27]. The main difference here is that in contrast to E-cadherin, N-cadherin signalling leads to cell repolarization[27] (FIG. 3), which is associated with the differential capacity of E-cadherin to bind to p120 and regulate the activity of small GTPses[27]. It remains to be seen whether switching between cadherin isoforms (so-called cadherin switching) is a general mechanism to control CIL capacity. However, it is interesting to note that the switch between E- and N-cadherin is observed during epithelial–mesenchymal transition (EMT) in neural crest and cancer cells[27,37], which may aid their invasiveness by modulating CIL behaviours (see the section 'Unexplored roles for CIL' below). In line with this finding, the differential binding of E- and N-cadherin to different p120 isoforms and the concomitant loss of E-cadherin in pancreatic carcinoma cells has been linked to the invasive potential of these tumour cells[38].

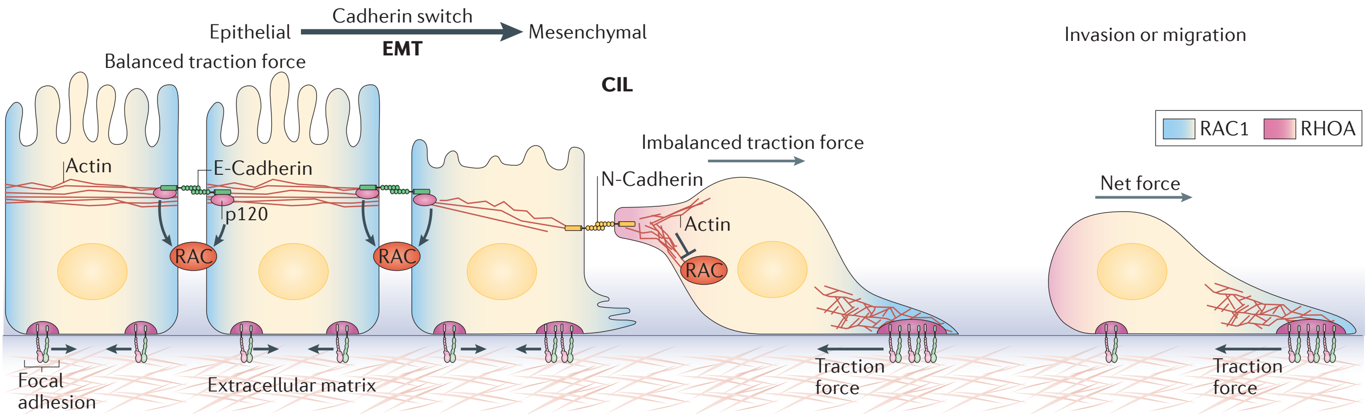

Figure 3 | **Cadherin switching in the regulation of epithelial–mesenchymal transition and contact inhibition of locomotion.** Epithelial–mesenchymal transition (EMT) involves a gain in migratory capacity along with a reduction in cell–cell adhesion, and this transition is controlled by a change in the type of cadherin molecules expressed at the cell surface. E-Cadherin generates stable intercellular adhesions between epithelial cells. Upon loss of E-cadherin and acquisition of N-cadherin, neural crest cells undergo EMT while simultaneously gaining a capacity for contact inhibition of locomotion (CIL)[27]. E-Cadherin suppresses EMT and CIL by signalling to other adhesion components, such as p120 catenin, which polarizes the small GTPase RAC1 towards cell–cell junctions, thereby inhibiting the protrusions at the cell contact. By contrast, N-cadherin expression promotes polarization of RAC1 activity towards the leading edge of cells in an epithelial sheet, which allows them to generate asymmetric traction stresses for directed migration away from neighbouring cells.

In addition to classical cell adhesion molecules, other receptor families have been implicated in establishing the initial contact during CIL (FIG. 2a). Eph receptors are a group of tyrosine kinase receptors that bind transmembrane ephrin ligands on neighbouring cells, and bidirectional signalling from these Eph–ephrin interactions mostly leads to a repulsive response[39]. In Cajal–Retzius cells, both EphA and EphB receptors are required for normal CIL behaviour, which is necessary for their dispersion[40]. EphA is also involved in homotypic CIL between prostate cancer cells, whereas EphB acts as a suppressor of heterotypic CIL between these cells and normal fibroblasts[41,42]. Thus, the balance of signalling mediated by different Eph receptors can determine the capacity of a cell for CIL. This is intriguing as the loss of CIL upon contact of cancer cells with normal cells is speculated to play a role in cancer metastasis[10], and in prostate cancer cells it has been shown that modulating Eph-ephrin signalling leads to a loss of CIL behaviour[41,43]. There may also be more complicated interactions between the various receptors involved in CIL. Crosstalk between Eph receptors and cadherins controls the compartmentalization of cells in epithelial tissues[44]. Furthermore, similar crosstalk has been observed during embryonic boundary formation in *Xenopus* mesoderm[45], which is hypothesized to involve a process analogous to CIL (see the section 'Unexplored roles for CIL' below).

Recently, SLIT–ROBO interactions have also been revealed to be involved in CIL between fibroblasts. ROBO receptors belong to the immunoglobulin superfamily of cell adhesion molecules, and SLITs function as their normally secreted ligands. NIH 3T3 mouse fibroblasts utilize ROBO4–SLIT2 signalling during CIL, with SLIT2 apparently tethered to the cell surface rather than secreted. Similar to Eph receptors, crosstalk between SLIT–ROBO and cadherins is possible[46,47], suggesting that receptor interactions may be a common theme during CIL.

Protrusion inhibition. A CIL response is initiated by interactions between actin-rich lamellae of colliding cells[16,25,26]. One of the main regulators of lamellar dynamics during cell migration are the small GTPases RHO, RAC and CDC42, which have also been implicated in CIL[25,27,41,48–51]. For example, collision of neural crest cells leads to an inhibition of RAC1 activity[25,48], which is dependent on N-cadherin and WNT–planar cell polarity (PCP) signalling[25,49]. Many PCP components, including Dishevelled, Prickle 1 and Strabismus (also known as Van Gogh-like 2), are recruited to the receptor Frizzled 7 at the cell–cell contact point, leading to the inhibition of RAC1 and activation of RHOA[25,27,49] (FIG. 2b). How RAC1 is inhibited is currently unclear, but it may occur indirectly through RHOA activation because these GTPases are antagonistic[52]. In addition, in neural crest cells another polarity molecule, partition defective 3 homologue (PAR3; also known as PARD3), implicated in the establishment of apical polarity in epithelia, becomes localized to the site of cell–cell contact during CIL. This is thought to inhibit the RAC1 activator TRIO[48], thereby contributing to RAC1 inhibition (FIG. 2b). Similarly, homotypic CIL between pancreatic cancer cells is controlled by EphA-mediated activation of Rho-associated protein kinase (ROCK) and RHOA. By contrast, loss of CIL observed upon heterotypic interactions between prostate cancer cells and fibroblasts involves EphB3 or B4 activation and induction of CDC42, which then leads to continued cell migration[41]. Finally, ROBO4–SLIT2 induction in fibroblasts during CIL controls the duration of RAC1 activity[50], and CIL between glial cells is dependent on RAC1 regulation by the guanine nucleotide exchange factor T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1)[53]. Thus, it appears that small GTPase regulation is a conserved aspect of CIL regulation in numerous cell types.

Eph–ephrin interactions
Interactions between a transmembrane receptor (Eph) and its membrane-bound ligand (ephrin), which can signal bidirectionally (that is, both receptor and ligand can induce intracellular signalling) to control behaviours such as cell repulsion.

Cajal–Retzius cells
A transient neuronal population established during embryogenesis that undergoes specific migration and spreading in the cortex of the brain, which controls the development of other neuronal cells.

SLIT–ROBO
A transmembrane receptor (ROBO) and its normally secreted ligand (SLIT) largely studied in the context of neuronal growth cone guidance.

Small GTPases
A family of proteins that includes RHO, RAC and CDC42, which are involved in the regulation of the cytoskeleton.

Planar cell polarity
(PCP). The polarization of cells within a sheet in a planar fashion, which involves a core set of components involving transmembrane proteins, such as Frizzled, and downstream signalling mediators, such as Dishevelled.

Glial cells
Cells supporting neuronal development and function in the central nervous system.

Formin
A family of proteins involved in polymerization of actin, which has been shown to regulate specific actin structures, and the organization of contractile cytoskeletal elements in cells such as stress fibres.

Microtubule catastrophe
The transition of a microtubule from a growth to a shortening phase.

Substrate traction stresses
Cells residing on elastic substrates will pull on the substrate and produce fine-scale deformations, which can be measured to estimate the stress that the cells exert on their extracellular matrix.

Focal adhesions
Specific adhesions that anchor cells to the substrate; they contain a complex of signalling proteins, such as focal adhesion kinase and paxillin, along with transmembrane proteins such as integrins.

Interference reflection microscopy
A microscopy technique for cells cultured *in vitro* that uses polarized light to highlight cell structures close to the substrate. This technique was first used to highlight points of cell–substrate adhesion (focal adhesions).

Contraction of protrusions and repolarization. Actomyosin-mediated contraction of protrusions is often observed during CIL. Similar to inhibition of protrusion activity, small GTPases also have an essential role in this stage of the response. In fibroblasts and *Xenopus* neural crest cells, this process occurs through RHOA–ROCK signalling[25,54], whereas in *Drosophila* macrophages (haemocytes), this process involves the RHOA-responsive formin Diaphanous[26]. In Abercrombie's initial discovery of CIL, he hypothesized that a build-up in intercellular lamellar tension occurs upon cell collision[55], which has recently been confirmed during CIL between Drosophila macrophages[26]. In *Drosophila* macrophages, the development of contractile stress involves the physical coupling of the flowing actin networks in colliding lamellae, suggesting that a mechano-chemical signalling mechanism is operating[26]. This tension could subsequently have a direct effect on cell repolarization. For example, in mesodermal cells generation of external tension by pulling with a cadherin coated magnetic bead can induce cell repolarization[56]. As mesodermal cells can undergo CIL[57,58], it would be interesting to determine whether tension during their CIL response is also required for their reorientation. In addition to actin, other cytoskeletal elements, such as microtubules, have been implicated in CIL in numerous cell types[26,48,54,59,60]. Microtubule targeting of the cell–cell contact in *Drosophila* macrophages is a hallmark of the response[26,59], and in fibroblasts and neural crest cells, engagement of the cell–cell adhesion during CIL induces microtubule catastrophe, which seems essential for cell repolarization[48,54,60]. However, the precise mechanisms by which microtubules control the CIL process are currently unclear.

It should be noted that the precise sequence of the events of contraction and repolarization is not clear. While in chick heart fibroblasts and *Drosophila* macrophages, protrusion collapse at the cell–cell contact seems to precede the formation of new protrusions away from the contact site[15,26,28] (FIG. 2c); however, this may not always be the case. In neural crest cells, for example, the formation of new protrusions precedes the loss of the cell–cell junction, and this repolarization is thought to be essential to generate sufficient tension for subsequent lamellar contraction and cell separation[27] (FIG. 2c).

Migration away from the collision. Once the cells contract their protrusions and repolarize, the final step in a prototypical type I CIL response is to migrate away from the collision. One could therefore speculate that there must be reorganization of cell–substrate traction stresses for this event to occur and might involve modification of integrin adhesions (focal adhesions). Indeed, it has been shown that CIL responses of *Drosophila* macrophages require some role for integrin adhesions[61]. Abercrombie was one of the first to visualize focal adhesions during cell motility by interference reflection microscopy[22]. However, when using this technique in fibroblasts undergoing CIL, he did not observe any gross change in adhesions before cell contraction[22] despite some earlier evidence to the contrary[62]. Meanwhile, *Xenopus* neural crest cells engaging in CIL reduce the number of focal adhesions in the vicinity of cell–cell contacts, as measured by observing changes in the distribution of focal adhesion components, such as focal adhesion kinase and paxillin[27,63]. This reduction in focal adhesions at the cell–cell contact site would then lead to a redistribution of the cell–matrix traction stresses to other parts of the cell, which is necessary for movement away from the colliding partner (FIG. 2c,d). These observations suggest that focal adhesion reorganization during CIL might be a cell-type-dependent phenomenon or may occur in only some types of CIL. Alternatively, the failure to observe focal adhesion changes in fibroblasts by Abercrombie may have been the result of limitations in the technique used to observe adhesions in these cells. Nevertheless, it is likely that cell–cell and cell–matrix adhesions engage in crosstalk during CIL, as both types of adhesions must be regulated for cells to successfully separate and migrate away. Indeed, there are many examples of crosstalk between these adhesion complexes in several cell types[64–70].

We have clearly come a long way since the initial discovery of CIL in terms of understanding the regulation of its various stages as numerous components have been identified to be involved in the process (FIG. 2e). What is clearly missing is how all of these diverse regulatory factors, from cadherins to focal adhesions, are integrated to induce a seamless response, and whether all cell types (or CIL types) share these same mechanisms.

Embryological functions of CIL

Although CIL might at first glance appear to be driven by a simple cell–cell interaction, it can have a powerful instructive role when occurring within a population of cells. Indeed, CIL is an excellent example of how simple rules can lead to emergent behaviours, which is a recurring theme in biological pattern generation. Numerous mathematical models have revealed the ability of CIL to generate patterns of cellular movements that recapitulate complex cellular patterning observed in *in vitro* experiments (BOX 2). However, as discussed in this section and summarized in FIG. 4, CIL is no longer just an *in vitro* phenomenon, as many research groups have recently revealed roles for this process during embryonic development.

Driving cellular dispersion. CIL has the capacity to disperse a cell population such that the cells are driven into free space (Supplementary information S5 (movie)) in a process Abercrombie termed "negative taxis" (REF. 71). There are many instances during embryogenesis in which a population of cells originates in a specific location and subsequently disperses to reach their final positions, and CIL can play a part in their spreading. This process is indeed what occurs during Cajal–Retzius cell migration (FIG. 4a). These cells are born in distinct regions of the brain and spread throughout the cerebral cortex, which is critical as Cajal–Retzius cells control the subsequent migration of other cell types. CIL dynamics between Cajal–Retzius cells, regulated by Eph–ephrin signalling, are sufficient to induce the spreading and final distribution of the population[40]. Repulsion between these cells is essential for their distribution, suggesting that they must be undergoing a type I kind of CIL behaviour.

Collective cell migration
A process whereby a collection of cells engages in coordinated motility such that they move as a coherent group.

Chemotaxis
The response of cells to an extracellular chemical signal, which induces their migration in a directed fashion.

Inducing cellular tiling. Although Cajal–Retzius cells distribute relatively evenly throughout the cerebral cortex, their distribution is not completely homogeneous[40]. However, there are many instances in the embryo in which cells adopt a highly even distribution, such as tiled arrays, and CIL can also be a driving factor of this process. *Drosophila* macrophages are an example of a cell type that disperses during embryogenesis, eventually adopting a more homogeneous distribution akin to tiling[59] (FIG. 4b). A combination of live imaging (Supplementary information S2 (movie)) and mathematical modelling showed that CIL is sufficient to explain the even spacing between *Drosophila* macrophages[59].

Box 2 | **Mathematical models of CIL explain 'social' cell behaviour**

Through studying CIL, Abercrombie developed a number of approaches to quantify the 'social behaviour' of cells in tissue culture, leading eminent scientists to call him "the pioneer ethologist of cells"[101]. He led cell biologists away from qualitative analyses and towards rigorous quantitation[102], and he would certainly be inspired by the numerous mathematical models recently developed to investigate CIL. These models have been essential in highlighting how this seemingly simple reaction can explain the emergent social behaviour of a population of cells, which lead to responses such as collective cell migration. It is unclear precisely why there has been a sudden increase in CIL models, but it is possible that cell biologists are taking a page from real ethologists who have developed mathematical models to explain the collective motion of animals. Three simple rules are required to explain animal flocking behaviour[103]: cohesion of the group, alignment of motion, and separation (a short range repulsion akin to CIL behaviour). Interestingly, many of the CIL collective motion models use similar parameters. These models have been used to better understand three types of coordinated cellular motion.

Spontaneous collective migration

Cells in culture often exhibit emergent coordinated patterns of movement, such as swirling and streaming[104], which, until recently, have been largely unexplained. Modelling has revealed that when one takes into account the inherent cellular behaviours involved in CIL (such as cell repolarization[21]) within a cell population, coordinated movements can spontaneously emerge[21,23,105–108]. In these cases, it is critical that CIL is integrated with other intercellular interactions, such as cell–cell adhesion[23,107] or chemotactic co-attraction[108]. Furthermore, CIL can lead to other features observed during collective cellular motion, such as the patterns of traction stress[109].

Collective chemotaxis

There are many examples during development whereby large groups of cells need to collectively migrate towards some external cue, and it is unclear how such populations of cells organize and move in a coordinated fashion. Models have revealed that CIL behaviour within a population can greatly increase the efficiency of this coordinated chemotaxis. Again, CIL must be integrated with other factors, such as co-attraction[110,111] or cell confinement[112], to collectively sense and migrate towards a chemotactic cue. In a recent twist, modelling revealed that an extracellular gradient capable of specifically modifying the strength of CIL between cells depending on the local concentration of the cue is sufficient to generate collective chemotaxis[113]. In this case, the chemotactic cue is controlling directed migration by specifically modifying CIL properties rather than directly controlling the migratory machinery of the cells.

Cellular dispersion and tiling

One final type of coordinated motion that modelling has revealed to involve CIL is the dispersion of a population of cells. In this case, simple rules controlling cell collision and subsequent repulsion are capable of driving the spreading of the population[40]. Moreover, depending on the precision of the CIL response (that is the consistency of the repulsion between cells during collisions), this process can even lead to a uniform cellular distribution akin to tiling[26,59]. This type of coordinated cellular motion explains the radial outgrowth of cells from an explant observed by Abercrombie and colleagues. Indeed, the same simple CIL rules used in a previous kinematic model to explain cellular tiling[59] is sufficient to simulate the radial outgrowth of cells from an explant (Supplementary information S5 (movie)).

The difference between CIL inducing simple spreading of a population versus cell tiling appears to be related to the precision of the CIL response. CIL between *Drosophila* macrophages is highly orchestrated, and collision dynamics are synchronized between colliding cells in terms of changes in cell motion. This precision is essential for their even spreading[26]. Mathematical modelling revealed that random deflections (for example, as a result of a type II CIL response) lead to reduced homogeneity of the population; indeed, perturbing the orchestration of *Drosophila* macrophage CIL prevents cell patterning[26]. It has been noted that Cajal–Retzius cell distribution shows regions of aggregation[72], which could be somewhat predicted by decreasing the CIL precision; therefore, it is possible that imprecise repulsive interactions are actually instructive for the final density of these aggregations.

Coordinating collective cell migration. As mentioned earlier, *in vitro* analysis of CIL has indicated that CIL can help to orchestrate the collective cell migration of a cell population, and neural crest cell migration during embryogenesis is an excellent example of this coordinating influence (FIG. 4c). Different neural crest cell populations migrate as coherent clusters or in linear chains during development, and *in vivo* experiments in both *Xenopus* and zebrafish have revealed that coherent movement of cell clusters is severely affected when CIL is absent[25]. Furthermore, *in vitro* analysis of epithelial cell migration coupled with mathematical modelling revealed that chain migration also emerges solely through CIL dynamics[23]. Cranial neural crest cells, for example, migrate towards a chemokine source (stromal cell-derived factor 1 (SDF1)), and the occurrence of CIL within the population is thought to restrain the formation of protrusions between neighbouring cells, thus allowing the entire population to acquire a single, coherent polarity necessary for their collective motion[49].

Interestingly, heterotypic CIL interactions between *Xenopus* and zebrafish neural crest cells and other cell types are also an instructive cue for tissue patterning during embryogenesis. For example, neural crest cells aid in the morphogenesis of epithelial placodes, which contribute to the formation of sensory organs (FIG. 4d). Neural crest cells are attracted to placodes by the placodal expression of SDF1. However, placodal cells undergo CIL in response to neural crest cells, and placodal cells are subsequently repelled to induce a chase-and-run behaviour. Neural crest cells also undergo CIL and repolarization in response to the contact with placodal cells; however, the CIL response of neural crest cells appears to be overridden by their attraction to SDF1, thus allowing the chase to continue[63]. This cooperation between CIL and chemotaxis has also been observed in breast cancer cells *in vitro*[73], suggesting that CIL integration with chemotactic cues may be a common theme in directing cell movement.

It is interesting to speculate why CIL leads to collective motion in some cell types but to cell dispersion in others. It is possible that the final outcome is related to specific behaviours associated with collision geometry.

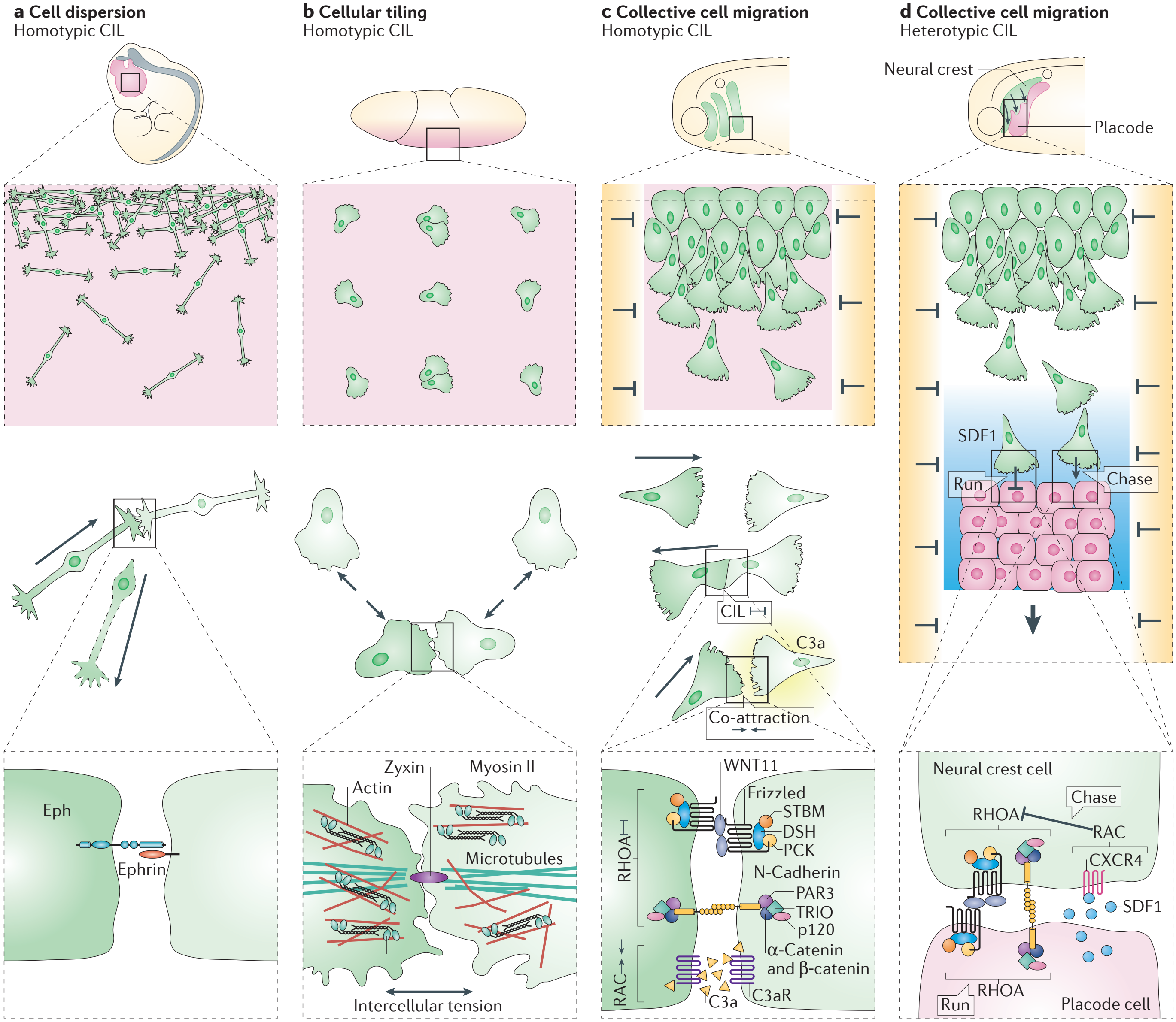

Figure 4 | **Embryological functions of contact inhibition of locomotion.** **a** | Contact inhibition of locomotion (CIL) drives the dispersion of Cajal–Retzius cells, a neuronal population in the cerebral cortex, during development[40]. The cells are initially clustered, but following Eph–ephrin-regulated CIL interactions they spread throughout the tissue in a manner similar to radial outgrowth from an explant (Supplementary information S5 (movie)). **b** | CIL controls the even spacing of *Drosophila* macrophages (haemocytes) during their developmental dispersal, which requires precisely orchestrated CIL interactions[26,59]. This CIL precision is regulated by the development of a cell–cell adhesion, as evidenced by the localization of the adhesion-marker Zyxin. Subsequent coupling of the myosin-driven flowing actin networks between colliding lamellae leads to the development of intercellular tension, which synchronizes cell repulsion[26]. **c** | Homotypic CIL interactions control the collective migration of neural crest cells[25,111]. CIL is triggered by the activation of two sets of receptors, Frizzled and N-cadherin, which leads to the activation of RHOA at the site of cell contact. Frizzled is a planar cell polarity (PCP) receptor that recruits WNT11, Strabismus (STBM), Dishevelled (DSH) and Prickle 1 (PCK). N-Cadherin recruits p120, α- and β-catenin, partition defective 3 homologue (PAR3) and triple functional domain protein (TRIO). Consequently, RAC1 is inhibited at the cell–cell contact site, leading to cell repolarization and cells moving away from each other. In neural crest cells, CIL behaviour is integrated with other intercellular responses, such as autocrine-mediated co-attraction by a chemoattractant, C3a (neural crest cells also express the C3a receptor (C3aR))[111], and chemotaxis[49] (not shown here) to allow for coherent motion of the population. **d** | Heterotypic CIL interactions also control the coordinated movement of neural crest and placodal cell populations[63]. Neural crest cells are attracted to placodal cells via the placodal expression of the chemoattractant stromal cell-derived factor 1 (SDF1). Placodal cells, as a result of CIL responses after contact with neural crest cells, undergo repulsion. Owing to these simultaneous attractive–repulsive interactions, the placodal and neural cells engage in a migratory mode termed chase-and-run behaviour. CIL between neural crest and placode cells involves the PCP receptor Frizzled (together with WNT11, STBM, DSH and PCK) and N-cadherin (together with p120, α- and β-catenin, PAR3 and TRIO) as described in part **c**, with the resulting activation of RHOA at the cell contact site and collapse of cell protrusions. The activation of C-X-C chemokine receptor type 4 (CXCR4) in neural crest cells by the placodal expression of SDF1 leads to activation of RAC and protrusion growth. Therefore, although neural crest cells initially collapse their protrusions, they are rapidly reformed to allow 'chase' of placode cells. By contrast, placodal cell protrusions completely collapse in response to neural crest cells, leading to the 'run' behaviour.

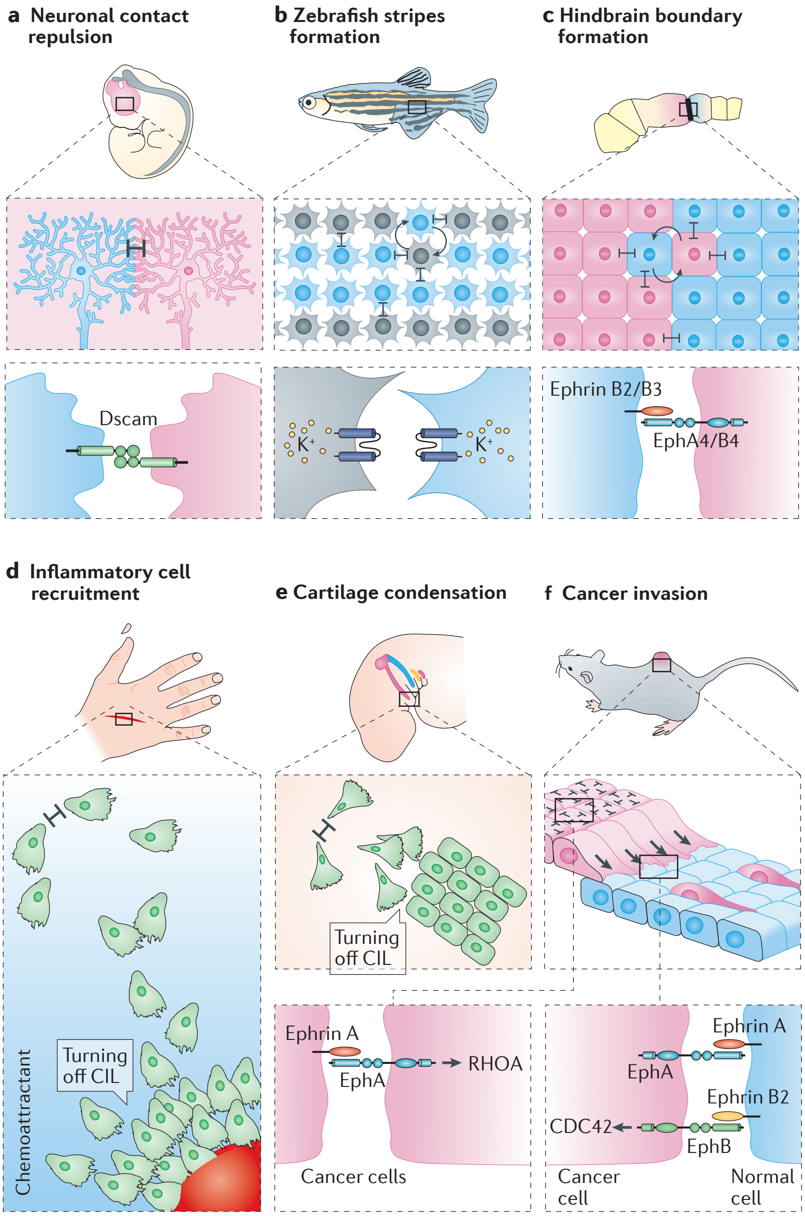

Figure 5 | **Unexplored roles for contact inhibition of locomotion. a** | Repulsion between neuronal cells, which has recently been termed 'contact repulsion', involves cellular interactions analogous to the contact inhibition of locomotion (CIL) described in this Review. These repulsive interactions may be involved in spacing neuronal cells bodies or preventing overlap of their dendrites to allow dendritic tiling (which is known to require transmembrane receptors such as Down syndrome cell adhesion molecule (Dscam))[79–82]. **b** | Formation of stripes in zebrafish skin involves the organized spacing of different pigment cell populations. The repulsion of pigment cells requires membrane depolarization through activation of an inwardly rectifying potassium channel (Kir7.1), which leads to intercellular interactions that appear identical to CIL[83–86]. **c** | The formation of boundaries between the various subcompartments of the hindbrain, which involves segmentation of cell populations, has been hypothesized to require CIL-like repulsive behaviours that prevent cell intermixing at the boundary interface[45,87–89]. Similar to CIL in other cell types, this repulsive behaviour at compartmental boundaries requires Eph–ephrin signalling. **d** | Insults such as wounding or infection necessitate the activation of immune cells and their aggregation at the damaged or infected site[94,96]. The ability of these cells to gather at these sites has been hypothesized to involve a reduction in their CIL capacity[95]. **e** | Cartilage condensation involves the coalescence of cells in the mesenchyme that may involve turning off CIL interactions, which initially might also be important for spreading of these cells in the embryo[90]. **f** | A loss of heterotypic CIL in cancerous cells may be involved in metastasis by aiding their invasiveness into neighbouring tissues[10,14,16,41,42,53,71]. It is also possible that enhanced cancer cell dissemination may be controlled by the simultaneous maintenance of homotypic CIL interactions between cancer cells, which would provide a driving force for the spreading of the cancer population in a fashion similar to CIL in cell dispersion[71]. Therefore, both a loss of heterotypic CIL and maintenance of homotypic CIL could be playing a part in the invasive potential of cancer cells. Homotypic CIL between prostate cancer cells is dependent on ephrin A–EphA receptor interactions, whereas interaction between EphB receptors present in these cancer cells and ephrin B2 in normal cells leads to activation of CDC42, and the consequent suppression of a CIL response.

For example, modelling of CIL in vertebrate epithelial and endothelial cells has revealed that the reduced CIL capacity during head-to-tail interactions in these cells leads to collective motion within the cell population[21,23]. However, this event may be cell-type dependent because *Drosophila* haemocytes fail to undergo CIL during head-to-tail interactions and disperse rather than show collective migration[26].

Unexplored roles for CIL

There are numerous physiological processes in which cellular behaviours suggest that CIL is involved. Notably, some of these examples are actually not that speculative because the associated cell behaviours involve stereotypical features of CIL responses that so far have not been linked to the phenomenon. Other 'speculative' roles were even historically identified as CIL behaviour (presumably during a time when studying CIL was in vogue), but have undergone recent nomenclature changes such that they are now considered to be distinct processes. Here, we provide a few examples (FIG. 5).

Neuronal contact repulsion. The nervous system is a good example where CIL is probably playing a part during several developmental events. Neuronal pathfinding involves both positive cues (such as chemotactic signals) and negative, repulsive signals[74]. Some of the repulsive varieties that neuronal growth cones experience during their guidance involve direct cell–cell contact, and this process has been termed 'contact repulsion' for the past decade. However, during Abercrombie's time, this same contact repulsion process was considered CIL behaviour[75–78].

More speculative roles for CIL in the nervous system involve neuronal patterning (FIG. 5a). There are examples in which neuronal populations develop into evenly

Neuronal growth cones
Dynamic, actin-rich structures at the termini of axons that control the migration of nerve cells.

spaced cellular arrays, such as in the retina[79], that one could imagine involves a similar CIL process to the tiling of *Drosophila* macrophages. Indeed, cell–cell contact-induced repulsive interactions have been shown to have a role in neuronal tiling[80]. Similarly, the development of dendritic fields, which involves spacing of not only neuronal cell bodies but also their dendritic projections, also requires contact-mediated mutual repulsion that one could consider to be a CIL response[81,82].

Stripe formation in zebrafish skin. The intricate patterning of zebrafish pigment cells involves a process of cell repulsion that is essentially the same phenomenon as CIL (FIG. 5b). The stripes in zebrafish skin are composed of three types of pigment cells (melanophores, xanthophores and iridophores) that tile into cellular arrays and segregate to form distinctly coloured lines. The pigment cells are migratory and undergo contact-dependent repulsive behaviour during stripe development, and this process is essential for the acquisition of the final pattern[83–85]. Furthermore, repulsive responses are unique depending on whether the pigment cell is interacting with a cell of its own type or another, suggesting that stripe formation is an example in which homotypic versus heterotypic CIL responses are also having a role[83,86]. Interestingly, this heterotypic pigment cell-repulsive response involves xanthophores chasing melanophores in a process the authors termed "run-and-chase" behaviour[83], which resembles the CIL-induced chase-and-run interaction between neural crest and placodal cells discussed above[63].

Tissue boundary formation. During embryogenesis, cells within tissues, such as in the hindbrain, are often segregated into distinct subdivisions in which cells are prevented from intermingling with neighbours at subdivision borders (FIG. 5c). The generation of these boundaries is controlled by several active processes, including differential adhesion, the generation of cortical tension at the border interface and cell repulsion[87]. This repulsive response (actually termed CIL in recent papers[45,87,88]) involves Eph–ephrin signalling[45,89], which, as discussed earlier, plays a crucial part in CIL in several other cell types.

Cell condensation. There may be instances in which turning off CIL behaviours may be instructive for a population of cells. Groups of mesenchymal cells during embryogenesis often need to condense to begin forming a coherent tissue, such as during cartilage development[90] (FIG. 5e). Assuming that the cartilage precursor cells initially spread through cell repulsion driven by CIL interactions, one means of inducing cell aggregation within the population may involve reducing or switching off the repulsive responses between the cells. This scenario is plausible because at least some cartilage precursors derive from neural crest cells, which are known to engage in CIL behaviours as discussed above.

Inflammatory cell recruitment. Embryogenesis is not the only physiologically relevant process in which CIL is involved. The immune system comprises a complex ecosystem of cell types that requires the dynamic regulation of cell interactions; it is therefore a good place to look for instructive roles for CIL. Indeed, one of the few migratory interactions that has been shown to completely fail in CIL is the collision between leukocytes (white blood cells) and fibroblasts[91,92], and it is possible that this failure in heterotypic CIL is essential to allow leukocyte migration to sites of infection or wounds (FIG. 5d). Interestingly, leukocytes still show CIL responses during collisions with each other[91], and the negative regulation of this homotypic CIL behaviour may also be playing a part during immune activation. As discussed above, *Drosophila* macrophages spread themselves uniformly within the animal[26,59,93], which may be essential for even immune system coverage. However, when wounding occurs, macrophages must aggregate at wound sites, and this aggregation must involve the modification of their normal repulsive behaviour[94]. Notably, recent modelling of *Drosophila* macrophage wound responses revealed that dampening CIL behaviour in these cells was essential for their recruitment[95]. It remains to be determined whether mammalian immune cells have the capacity to modulate their CIL responses, but it is interesting to speculate that processes such as immune cell swarming during infections[96] involve changes in repulsive behaviour to enable such cell aggregation.

Cancer invasion. Abercrombie speculated about the roles for CIL in animal physiology, and his most provocative ideas were regarding CIL in cancer metastasis[10,14,16,71] (FIG. 5f). He discovered that many cancer cells lost their ability to undergo CIL — not upon contact with each other as many have incorrectly stated — but in response to other, non-transformed cells[69]. Indeed, he noted that total failure in CIL has only been observed in a few heterotypic interactions, such as the interaction between sarcoma cells (cancer cells of the connective tissue) with fibroblasts[11] (Supplementary information S4 (movie)). It must be clear that he did not suggest cancer cells lost their CIL capacity entirely as many cancer cells still maintain homotypic CIL. He therefore also realized that homotypic repulsion between cancer cells "would greatly increase the efficiency with which the population spreads" (REF. 71) (Supplementary information S5 (movie)). Indeed, metastatic processes such as EMT involve a loss of epithelial characteristics and an acquisition of mesenchymal traits (such as the possibility for an enhanced CIL capacity) (FIG. 3). Thus, it is interesting to hypothesize that an increase in homotypic CIL responses could be playing a part in the initial spreading of cancer, similar to the spreading of neural crest cells[27].

Despite much speculation about CIL in cancer, the molecular mechanisms involved in modulating CIL behaviour during homotypic and heterotypic cancer cell interactions is largely unexplored. For example, it is currently unclear whether the E- to N-cadherin switch (FIG. 3), which is widely observed during EMT in cancer, has a role in modulating CIL behaviour during metastasis. Furthermore, despite several recent *in vitro* studies confirming a loss of heterotypic CIL in cancer cells[41,42,53], it still remains to be seen whether this also occurs in cancers *in vivo*. As cancer progression is now amenable to live imaging[97], it is time to revisit Abercrombie's ideas.

Dendritic fields
The development of an array of neuronal processes called dendrites in which individual cells cover specific, non-overlapping spatial territories.

Mesenchymal cells
Cells of embryonic origin that exist in connective tissues throughout the body and develop into a broad range of cell types, such as cartilage and bone.

Immune cell swarming
A process whereby collections of white blood cells, such as neutrophils, become activated and show coordinated chemotaxis and cluster formation, which is reminiscent of the swarming behaviour of insects.

Conclusion

The process of CIL is being rediscovered both as a model to address fundamental questions in cell biology and as a signal to control the movement and organization of cells during many physiological processes. Although we have come a long way in terms of discovering the molecular components implicated in CIL, what is currently missing is an understanding of how all of these factors are coordinated and, importantly, how they all fit into the overall dynamics of the process.

CIL behaviour, particularly the active type I variety, cannot be explained by simple signalling paradigms and must involve more complex mechano-chemical processes that modulate both cell motility and subsequent repolarization. The challenge now will be to understand how rapid cytoskeletal and signalling dynamics are propagated both spatially and temporally in the cell to ultimately induce cell repolarization. This challenge is not trivial, as it involves bridging temporospatial scales, which is experimentally and theoretically challenging and something that the cell motility field in particular is currently struggling with[2]. Furthermore, as CIL has recently been identified in a diverse range of cell types we are starting to revisit a problem that Abercrombie and colleagues came across decades ago: the precise definition of CIL. It may be that Abercrombie's final definition, "a cessation of forward motion upon migratory collision", is adequate. However, as this definition encompasses such a wide range of ultimate responses, it may become so broad that it is rendered useless on its own. One solution is to reconsider the idea that there are types of CIL responses that may each have distinct steps and regulatory mechanisms. What will help in this classification endeavour is the precise characterization of CIL behaviours in different contexts and in distinct cell types. Indeed, the more CIL behaviours that are identified, the easier it will be to categorize these responses and to extrapolate their underlying mechanisms, as well as their functions, from one cell type to the next.

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