© 2014. Published by The Company of Biologists Ltd | Development (2014) 141, 4199-4205 doi:10.1242/dev.101071

DEVELOPMENT AT A GLANCE

Chemokine signaling in development and disease

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ABSTRACT

Chemokines are a group of small, secreted molecules that signal through G protein-coupled receptors to promote cell survival and proliferation and to provide directional guidance to migrating cells. CXCL12 is one of the most evolutionary conserved chemokines and signals through the chemokine receptor CXCR4 to guide cell migration during embryogenesis, immune cell trafficking and cancer metastasis. Here and in the accompanying poster, we provide an overview of chemokine signaling, focusing on CXCL12, and we highlight some of the different chemokine-dependent strategies used to guide migrating cells.

KEY WORDS: GPCR, Cell migration, Chemokine, CXCL12, CXCR4

Introduction

Chemokines, or chemotactic cytokines, were initially discovered for their role in attracting immune cells to sites of inflammation (Oppenheim et al., 1991). However, subsequent studies have shown that chemokine signaling also guides the migration of neurons, neural crest cells and germ cells during embryonic development, regulates the patterning and remodeling of the vascular system, and attracts cancer cells to distant sites during metastasis (Lewellis and Knaut, 2012; Mayor and Theveneau, 2013; Raz, 2003; Bussmann et al., 2011; Cha et al., 2012; Cojoc et al., 2013; Orimo et al., 2005; Petit et al., 2007; Siekmann et al., 2009). To date, more than 50 chemokine ligands and 18 chemokine receptors have been described in human and mouse. Chemokine ligands are classified according to structure; most contain four cysteine residues that form two disulfide bridges, and they are divided into four classes based on the spacing between the first two of these cysteine residues: CC, CXC, CX3C and XC (Bachelerie et al., 2014). Chemokine receptors, which belong to the seven-transmembrane G protein-coupled receptor (GPCR) family, are named according to the class of chemokine ligand to which they bind. For example, the CXCR4 and CXCR7 receptors bind the chemokine CXCL12 (also known as stromal derived factor 1 or SDF1) (Balabanian et al., 2005; Bleul et al., 1996a; Burns et al., 2006), and the CCR7 receptor binds CCL19 and CCL21 (Yoshida et al., 1997, 1998). Most chemokine receptors couple to G proteins (Allen et al., 2007), although a few

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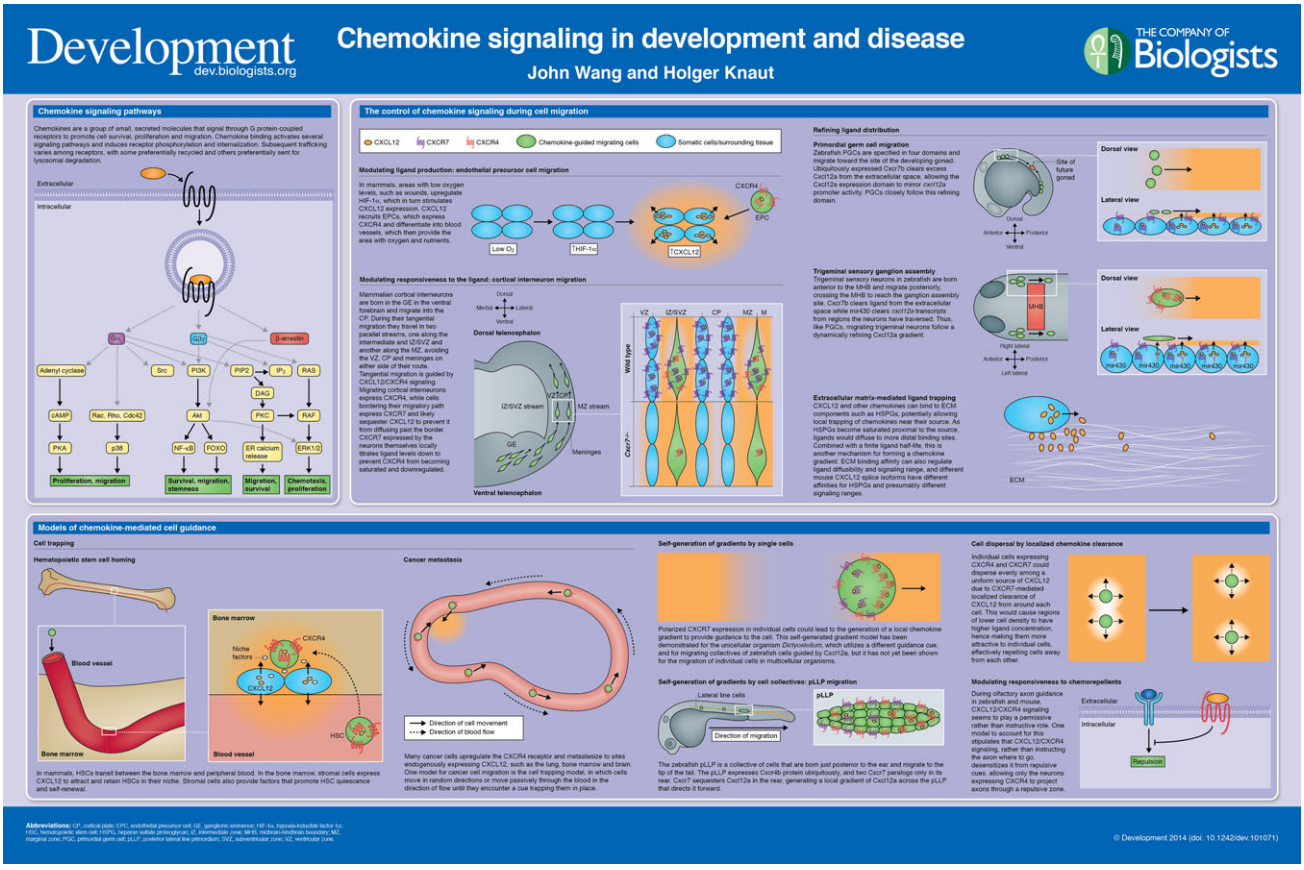

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act independently of G proteins and are instead thought to act as chemokine scavenger receptors or to signal through β-arrestin (Nibbs and Graham, 2013).

Chemokines are specific to vertebrates. Phylogenetic analyses suggest that basal chordates (cephalochordates and tunicates) lack chemokines, but that they are present in jawless fishes and higher vertebrates (Bajoghli, 2013; DeVries et al., 2006). In higher vertebrates, chemokines have expanded in number, such that even closely related species like human and mouse differ in their repertoire of chemokine ligands (Nomiyama et al., 2012). One of the most evolutionarily conserved chemokine signaling axes is the CXCL12/CXCR4/CXCR7 system, which has orthologs in vertebrate species ranging from jawless fishes to humans (DeVries et al., 2006). Here and in the accompanying poster, we use the CXCL12/CXCR4/CXCR7 system to provide an overview of general chemokine signaling strategies during development and in the context of cancer metastasis.

Mechanisms of CXCL12 signaling

CXCL12 binds to CXCR4 to activate a number of downstream signaling cascades primarily mediated through heterotrimeric G proteins and β-arrestins. G proteins are composed of three subunits: Gα, Gβ and Gγ. Ligand binding leads to the exchange of GDP for GTP in the Gα subunit, resulting in dissociation of the trimer into an active GTP-bound Gα and a Gβγ dimer. Activated G proteins signal through the phosphoinositide-3 kinase (PI3K)/Akt, inositol-1,4,5-trisphosphate (IP_3), mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) pathways to converge on growth-promoting pathways or to promote migration through the mobilization of intracellular calcium (Cojoc et al., 2013). In addition to signaling through G proteins, activated receptors recruit β-arrestin, which can lead to G protein-independent activation of Akt and ERK1/2.

The duration of CXCR4 signaling is regulated on two levels. First, receptor-ligand binding leads to the phosphorylation of CXCR4 by PKC and G protein-coupled receptor kinases (GRKs) (Busillo et al., 2010; Mueller et al., 2013). Phosphorylated receptors are rapidly internalized by β-arrestin and ubiquitylated by the E3 ligase AIP4, which targets them for lysosomal degradation (Marchese and Benovic, 2001; Marchese et al., 2003). Thus, CXCL12 signaling reduces CXCR4 receptor levels in CXCR4-expressing tissues (Donà et al., 2013; Sánchez-Alcañiz et al., 2011; Venkiteswaran et al., 2013). Second, regulators of G protein signaling (RGS) proteins enhance the GTPase activity of the Gα subunit, promoting GTP hydrolysis. The resulting GDP-bound Gα re-associates with the Gβγ dimer to return to an inactive state (Cojoc et al., 2013). Both mechanisms lead to the termination of signaling.

In addition to binding to CXCR4, CXCL12 binds to the non-canonical CXCR7 receptor. Depending on the context, CXCL12-CXCR7 binding is thought to result in two different responses: ligand internalization followed by ligand degradation (chemokine clearance), and β-arrestin-mediated G protein-independent signaling. Several observations support a role for CXCR7 in chemokine clearance. For example, CXCR7 does not associate with heterotrimeric G proteins, and ligand binding does not evoke calcium influx (Burns et al., 2006; Hoffmann et al., 2012). In addition, CXCR7 binds CXCL12 with a ten times higher affinity than CXCR4, and the receptor is rapidly recycled back to the plasma membrane upon ligand-induced internalization (Burns et al., 2006). These observations suggest that CXCR7 can act as an efficient chemokine sink because it can successfully compete with CXCR4 for access to the ligand, and a single receptor can undergo multiple rounds of ligand-induced internalization to target CXCL12 for degradation. G-protein-independent signaling through β-arrestins has also been demonstrated in several systems, including in interneurons, where CXCR7 elicits pERK signaling to modulate cell fate (Vogt et al., 2014; Wang et al., 2011).

As CXCR4 and CXCR7 both interact with β-arrestins, the relative levels of these two receptors in a cell can influence whether downstream signaling is preferentially mediated through β-arrestin-linked pathways or through G protein pathways (Coggins et al., 2014; Decaillot et al., 2011; Sierro et al., 2007). Moreover, CXCL12 can bind to CXCR4 as a monomer or as a dimer *in vitro*. Monomeric CXCL12 induces calcium influx and chemotaxis, whereas dimeric CXCL12 also induces calcium influx but lacks chemotactic activity (Drury et al., 2011; Veldkamp, 2005; Veldkamp et al., 2008). As higher ligand concentrations favor ligand dimerization, this suggests that the concentration of CXCL12 in the extracellular space could regulate which downstream signaling pathways are activated by CXCL12 binding to CXCR4 and CXCR7.

CXCL12 signaling in development and disease

CXCL12 guides many migrating cells and tissues, acting as an attractant to recruit or retain migrating cells. Cells migrating singly, such as primordial germ cells (PGCs) (Ara et al., 2003; Doitsidou et al., 2002; Knaut et al., 2003; Molyneaux et al., 2003), lymphocytes (Bleul et al., 1996a,b; Ma et al., 1998; Nagasawa et al., 1996; Zou et al., 1998), gonadotropin-releasing hormone (GnRH) neurons (Schwarting, 2006), endothelial precursor cells (Li et al., 2012), cardiomyocytes during heart regeneration (Itou et al., 2012), interneurons (Li et al., 2008; López-Bendito et al., 2008; Stumm et al., 2003; Tiveron et al., 2006), granule cells in the cerebellum and dentate gyrus (Bagri et al., 2002; Lu et al., 2002; Ma et al., 1998; Reiss et al., 2002; Zhu et al., 2002; Zou et al., 1998) and hematopoietic stem cells (HSCs) (Kawabata et al., 1999; Nie et al., 2008; Peled, 1999; Sugiyama et al., 2006; Tzeng et al., 2011), rely on CXCL12 to reach their target or remain at a distinct location. Similarly, cells migrating in small groups or as tissues, such as trigeminal sensory neurons (Knaut et al., 2005), sprouting blood vessels (Bussmann et al., 2011; Siekmann et al., 2009), the posterior lateral line primordium (pLLP) (David et al., 2002), the endoderm (Mizoguchi et al., 2008; Nair and Schilling, 2008) and some cancer cells, also use CXCL12 for guidance (Müller et al., 2001). Below, we outline several of these examples of CXCL12-mediated cell migration to highlight the conceptually different ways in which organisms employ CXCL12 to guide migrating cells and tissues.

Angiogenesis

Endothelial precursor cells (EPCs, or angioblasts) are migratory cells that form blood vessels. In mice, a subset of EPCs expresses CXCR4 and, in response to CXCL12, migrates towards target tissues, where the EPCs then differentiate and form new blood vessels (Li et al., 2012). This process occurs during embryonic development, in response to ischemia or wound repair in adults and during blood vessel formation in cancer (Li et al., 2012; Moschetta et al., 2014; Schmidt et al., 2007). During mouse development, for example, CXCR4-mediated CXCL12 signaling is required to guide EPCs during the formation of the aorta (Schmidt et al., 2007). In ischemic tissues in adult mice, low oxygen stabilizes the transcription factor hypoxia-inducible factor 1α (HIF-1α), which upregulates CXCL12 expression to recruit EPCs (Petit et al., 2007). Similarly, many cancers induce the expression of CXCL12 in stromal fibroblasts to

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attract EPCs to form new vessels, which provide oxygen to the growing tumor (Orimo et al., 2005).

Cortical interneuron migration

Cortical interneurons are a population of inhibitory neurons that mediate synaptic inhibition to shape cortical networks and support many brain functions. During mouse embryonic development, they migrate from their birthplace on the ventral side of the forebrain to the cortex and then undergo tangential migration, migrating in parallel to the cortical surface to distribute themselves throughout the cortex before undergoing radial migration to arrange themselves in specific cortical layers (Marín and Rubenstein, 2003). During tangential migration, cortical interneurons express both CXCR4 and CXCR7 (Daniel et al., 2005; Ray et al., 2012; Sánchez-Alcañiz et al., 2011; Stumm et al., 2007) and move towards sources of CXCL12 (Li et al., 2008), and CXCR4 signaling is necessary for this migration (Li et al., 2008; López-Bendito et al., 2008; Stumm et al., 2003; Tiveron et al., 2006).

Primordial germ cell (PGC) migration

PGCs, which give rise to sperm and eggs, are specified early during embryonic development and migrate from their birthplace in the early embryo to the future site of the gonad (Raz, 2003). The dynamic environment of the developing embryo provides a challenge for guiding germ cells because tissues are constantly moving and growing, potentially altering the distribution of guidance cues. In mice and zebrafish, PGCs express the CXCR4 or zf Cxcr4b receptor (zebrafish genes/proteins will be indicated by the prefix zf), respectively, and closely follow dynamically changing sources of CXCL12/zf Cxcl12a (Ara et al., 2003; Doitsidou et al., 2002; Knaut et al., 2003; Molyneaux et al., 2003). During PGC migration in zebrafish, changes in zf *cxcl12a* promoter activity are mirrored by similar dynamics on the transcript and protein level through microRNA-mediated zf *cxcl12a* transcript degradation (Staton et al., 2011), which remains controversial (Goudarzi et al., 2013; Staton et al., 2013), and through zf Cxcr7b-mediated zf Cxcl12a protein clearance (Boldajipour et al., 2008).

Trigeminal neuron migration

Trigeminal sensory neurons form the fifth cranial nerve, which relays sensory input from the face. They are born anterior to the midbrain-hindbrain boundary (MHB) as single dispersed cells. In zebrafish, these neurons, which express zf Cxcr4b, migrate in response to zf Cxcl12a and Cxcl12b (collectively referred to as zf Cxcl12) to assemble into a tight ganglion posterior to the MHB (Knaut et al., 2005). Although trigeminal sensory neurons encounter several zf Cxcl12-expressing tissues during their migration, they ignore them and only follow the zf Cxcl12 domain at the ganglion assembly site. This process requires tight control of the distribution of zf Cxcl12a through microRNA-mediated zf *cxcl12a* transcript degradation and through zf Cxcr7b-mediated zf Cxcl12a protein clearance (Lewellis et al., 2013).

Hematopoietic stem cell (HSC) trafficking

HSCs are adult stem cells that give rise to the entire blood lineage, including immune cells, red blood cells and platelets. They transit between the bone marrow and peripheral blood vessels, although the majority is located in the bone marrow (Bhattacharya et al., 2009; Wright et al., 2001). HSCs in mice and humans express CXCR4. They are attracted to their niche in the bone marrow by CXCL12 that perivascular cells secrete (Ding and Morrison, 2013; Greenbaum et al., 2013). CXCL12 levels in the bone marrow thus correlate with HSC levels; CXCL12 production in perivascular cells is higher during periods of rest – daytime for mice or nighttime for humans – and therefore there are one-fifth as many HSCs in the peripheral blood during periods of rest compared with periods of high activity (Méndez-Ferrer et al., 2008).

Posterior lateral line primordium (pLLP) migration

The lateral line system in fish is composed of a collection of neuromasts that detect the direction of water flow. The initial set of neuromasts is deposited by migrating primordia. One such primordium is the zebrafish pLLP, a collective of ∼100 cells that is born behind the ear and migrates along the body to the tip of the tail, periodically depositing neuromasts along its route (Ghysen and Dambly-Chaudière, 2007). Although zf *cxcr4b* transcripts are enriched in the front of the primordium (Aman and Piotrowski, 2008; David et al., 2002), zf Cxcr4b protein is expressed in all cells in the primordium (Donà et al., 2013; Venkiteswaran et al., 2013). By contrast, zf Cxcr7a and zf Cxcr7b are only expressed in the cells in the rear of the primordium (Valentin et al., 2007; Venkiteswaran et al., 2013). The zf Cxcl12a clearance activity of the two zf Cxcr7 paralogs serves as a local chemokine sink and generates a zf Cxcl12a concentration gradient across the primordium, providing it with directionality and propelling it forward (Donà et al., 2013; Venkiteswaran et al., 2013).

Cancer metastasis

It has long been noted that certain types of cancer cells metastasize to specific sites in the body (Paget, 1889). For example, human breast cancers commonly metastasize to bone marrow, lung, liver and brain (Nguyen et al., 2009). These sites of metastases often naturally express the cognate ligands for the chemokine receptors that are upregulated by the cancer cells. For example, breast cancer cells frequently upregulate CXCR4 and CCR7, and metastasize to organs expressing the respective CXCL12 or CCL19 and CCL21 ligands (Müller et al., 2001). Similar to immune cell trafficking, metastasizing cancer cells are thought to passively circulate in the vasculature until encountering a local chemokine source. Chemokine signaling is also thought to increase the affinity of cancer cells for endothelial cells and promote blood vessel extravasation and tissue invasion.

The versatility of chemokine-guided cell migration

Providing guidance to migrating cells poses many challenges to the organism. A limited number of cues guide hundreds of cells, and different types of cells with different destinations often migrate at the same time and in close proximity to one another. Moreover, cells often need to navigate over long distances and through dynamic environments. As we discuss below, the organism handles these challenges by tailoring the availability of the guidance cues to specific cell migration events.

Chemokine ligand availability, the availability of CXCL12 in this case, can be regulated on two different levels: production and distribution. Although there is no evidence for regulation of CXCL12 secretion, some CXCL12 expression domains are very dynamic, suggesting tight control of CXCL12 promoter activity and CXCL12 transcript stability. Indeed, CXCL12 transcripts are subject to microRNA-mediated degradation, and this has been shown to expedite transcript clearance from former sites of chemokine expression (Lewellis et al., 2013; Staton et al., 2011). Meanwhile, the distribution of CXCL12 is controlled by CXCL12 binding partners, CXCL12-inactivating proteins and CXCR7 receptor-mediated ligand clearance. Binding partners affect the spread of

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CXCL12; within a given time frame strong binding restricts CXCL12 to its source tissue such that it can only signal over a short range, whereas weak or no binding allows CXCL12 to diffuse and signal over a longer range. However, little is known about CXCL12 binding partners. *In vitro*, CXCL12 binds to heparan sulfate proteoglycans (Laguri et al., 2008), suggesting that the distribution of extracellular matrix components could restrict the distribution of CXCL12 *in vivo*. Moreover, different mouse alternative splice isoforms of CXCL12 have been demonstrated to have different affinities for heparan sulfate, presumably resulting in different diffusion and signaling ranges (Laguri et al., 2007). Inactivating proteins affect the range of CXCL12 signaling by reducing ligand half-life. Several proteases, including matrix metalloprotease 2 (MMP-2), neutrophil elastase and dipeptidylpeptidase 4 (DPP-4 or CD26), have been shown to cleave CXCL12 *in vitro* (McQuibban et al., 2001; Sun et al., 2008; Valenzuela-Fernández et al., 2002), suggesting that these enzymes could also control the activity of CXCL12 *in vivo*. Receptor-mediated CXCL12 clearance locally refines chemokine distribution and levels or acts globally to reduce CXCL12 perdurance. For example, CXCR7-mediated CXCL12 clearance is emerging as a mechanism for regulating ligand distribution (Abe et al., 2014; Boldajipour et al., 2008; Donà et al., 2013; Lewellis et al., 2013; Memi et al., 2013; Sánchez-Alcañiz et al., 2011; Venkiteswaran et al., 2013). CXCR7 binds, internalizes and targets CXCL12 for degradation, and this clearance function is used in a number of ways to sculpt the distribution of CXCL12.

Different combinations of the above mechanisms are used to regulate CXCL12-guided cell migration during development. In its simplest form, CXCL12 is expressed by the target tissue and diffuses to form a gradient that attracts cells. This classical mode of chemotaxis might underlie zebrafish olfactory placode assembly and olfactory axon targeting (Miyasaka et al., 2007). A variation of this mechanism is used to guide zebrafish PGCs and trigeminal sensory neurons; these cells closely follow a shifting zf Cxcl12a expression domain that progressively guides them towards their destination (Boldajipour et al., 2008; Lewellis et al., 2013; Staton et al., 2011). MicroRNA-mediated zf *cxcl12a* transcript clearance and zf Cxcr7b-mediated zf Cxcl12a clearance from past sites of zf *cxcl12a* expression are thought to ensure that the dynamic changes in zf *cxcl12a* transcription are mirrored by similar changes at the protein level (Boldajipour et al., 2008; Lewellis et al., 2013; Staton et al., 2011). In this context, the migrating cells remain closely associated with the rapidly shifting zf *cxcl12a* expression domain such that they rarely encounter other zf Cxcl12 sources that could erroneously guide them to the wrong location.

Although it is also a directed migration event, the guidance of the zebrafish pLLP is conceptually different. This cohort of cells migrates along a stripe of zf Cxcl12a expression (David et al., 2002). The cells in the rear of the primordium express zf Cxcr7 paralogs and clear zf Cxcl12a, generating a local zf Cxcl12a gradient across the collective to provide it with directionality (Donà et al., 2013; Venkiteswaran et al., 2013). Biophysical considerations suggest that a simple source-sink mechanism cannot establish a stable gradient over more than a few hundred microns within a reasonable time frame (Crick, 1970), thus seemingly precluding long-range directed migration. Self-generated attractant gradients sculpted from a uniform stripe of attractant bypass this physical limitation, allowing for long-range directed migration limited only by the length of the attractant stripe. In theory, a singly migrating cell could employ a similar mechanism by sorting CXCR7 to its rear to reinforce an existing gradient or to generate a new gradient across itself. Migrating *Dictyostelium* cells use this strategy, albeit with a different signaling system, secreting a phosphodiesterase to inactivate the attractant cAMP behind them (Garcia et al., 2009).

An alternative use for constitutive CXCL12 expression is to retain cells in a certain location or to trap cells that pass by. For example, CXCL12 acts as a retention signal for external germinal layer cells in the mouse cerebellum, and it is thought that inhibiting CXCR4 signaling allows these cells to escape retention (Lu et al., 2001; Zhu et al., 2002). A possible role for CXCR7 in escaping the retention of CXCL12 has not been reported. However, it has been suggested that downregulation of CXCR7 expression in the cortical plate and in cortical interneurons allows these interneurons to switch from tangential to radial migration by desensitizing them to CXCL12 attraction (Wang et al., 2011).

Opposite to escaping retention, in the case of HSCs and metastasizing cancer cells, local sources of CXCL12 are thought to trap cells that pass by the chemokine-expressing tissue and retain them (Anders et al., 2014; Zlotnik et al., 2011). Additionally, migrating cells can use CXCR7 to adjust their sensitivity to levels of CXCL12 in their surroundings. Tangentially migrating interneurons use this mechanism to maintain CXCL12 at a low enough concentration around them to prevent complete internalization and degradation of CXCR4 and to remain sensitive to the chemokine (Abe et al., 2014; Sánchez-Alcañiz et al., 2011).

Theoretically, this mechanism could also be used to ensure dispersal of migrating cells across a CXCL12-expressing tissue: a local reduction in CXCL12 levels, mediated by CXCR7-expressing migrating cells, will create a local dip in chemokine levels such that cells will move away from one another towards higher CXCL12 concentrations.

Attractant gradients do not need to be generated solely through the diffusion of the attractant from a local source. Graded binding or graded expression of the attractant can also generate an attractant gradient to guide migrating cells. This mechanism seems to be used by migrating dendritic cells, which crawl up an immobilized gradient of CCL21 (Weber et al., 2013), and by GnRH neurons, which seem to follow a graded expression of CXCL12 (Schwarting, 2006). In the latter case, the graded expression of CXCL12 seems to be refined by an opposing graded expression of CXCR7 (Memi et al., 2013).

Finally, CXCL12 signaling can interact with other signaling pathways to guide migration events. For example, during zebrafish olfactory axon targeting, zf Cxcl12a seems to play a permissive rather than instructive role, which has led to the suggestion that it modulates the sensitivity of the axon growth cone to a nearby repulsive cue (Miyasaka et al., 2007).

Conclusion

Over the past decades, it has become clear that chemokines can act as attractants and form gradients to guide a plethora of migrating cells. Organisms solve the problem of guiding hundreds of cells with only a few cues by reusing the same guidance cues for multiple migration events. This requires careful control over the distribution of the guidance cue. More recent studies indicate that the precise control of chemokine production and diffusion can tailor chemokine availability to properly direct migrating cells. However, the mechanisms that control the production and diffusibility of chemokines remain largely unexplored. Moreover, it is not clear how migrating cells tune their chemokine receptors and downstream signaling pathways to the presence of chemokines. Finally, we lack a biophysical description of chemokine diffusion and cellular chemokine perception. Given the important role of chemokine signaling in immune system disorders (Zlotnik and Yoshie, 2012)

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and cancer (Dorsam and Gutkind, 2007; Zlotnik et al., 2011), and its emerging role in psychiatric disorders such as schizophrenia (Meechan et al., 2012; Toritsuka et al., 2013), an understanding of these issues is crucial. With advances in light microscopy and quantitative measurements, such fundamental questions should become addressable in the future.

Acknowledgements

We thank D. Nagelberg, G. Venkiteswaran, T. Colak, C. Nicholson, F. Schnorrer and the three anonymous reviewers for critical comments and insightful suggestions. We apologize to authors whose work we were unable to cite as a result of space constraints.

Competing interests

The authors declare no competing financial interests.

Funding

This work was supported by grants from the National Institutes of Health [NS069839 to H.K. and HD007520 to J.W.]. Deposited in PMC for release after 12 months.

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A high-resolution version of the poster is available for downloading in the online version of this article at http://dev.biologists.org/lookup/suppl/doi:10.1242/dev.101071/-/DC1.

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