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Modeling factors that regulate cell cooperativity in the zebrafish posterior lateral line primordium

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ABSTRACT

Collective cell migration is an integral part of organismal development. We consider migration of the zebrafish primordium during development of the posterior lateral line, a sensory system that detects water movement patterns. Experiments have shown that the chemokine ligand CXCL12a and its receptors CXCR4b and CXCR7b are key players for driving migration of the primordium, while FGF signaling helps maintain cohesion. In this work, we formulate a mathematical model of a laser ablated primordium separated into two smaller cell collectives: a leading collective that responds to local CXCL12a levels and a trailing collective that migrates up a local FGF gradient. Our model replicates recent experimental results, while also predicting a "runaway" behavior when FGF gradient response is inhibited. We also use our model to estimate diffusion coefficients of CXCL12a and FGF in the lateral line.

1. Introduction

Collective cell migration is an essential process during organismal development. Put simply, groups of cells need to be transported to specific locations in order to perform specific functions (Weijer, 2009). Often, cells require a chemical signal to guide their movement (chemotaxis). For example, chick neural crest cells are guided by growth factors, melanoma cells are guided by lysophosphatic acid (LPA), and *Dictyostelium* cells aggregate by secreting and following gradients of cyclic AMP (Ferguson et al., 2016; Tweedy et al., 2016; Weijer, 2009). Although collective cell migration has been studied extensively in these and other contexts, many open questions remain, including:

- How are signaling gradients formed and maintained by migrating cells?
- How do cells "read" signaling gradients?
- Do all cells in a collective sense a chemotactic signal, or do only leader cells sense the signal and direct follower cells?

The zebrafish posterior lateral line, a sensory network that detects water movement patterns, is an excellent system for studying the mechanisms that drive collective cell migration. Crucial to development of the lateral line is directed migration of the zebrafish posterior lateral line primordium, a collective of about 100 cells that migrates from the otic vesicle at the head of the fish to the tip of the tail along the horizontal myoseptum, a midbody tissue layer (Ghysen and Dambly-Chaudière, 2007). As it moves, the primordium periodically deposits rosette-shaped neuromasts, mechanosensory organs made up of a central hair cell surrounded by support cells. The lateral line is composed of 4–5 neuromasts along the surface of the body and 2–3 neuromasts at the tip of the tail (Aman and Piotrowski, 2011).

Movement of the primordium is driven by the chemokine ligand CXCL12a, also known as SDF1α, and its receptors CXCR4b and CXCR7b. The primordium follows a narrow stripe of CXCL12a expressed by muscle pioneer cells of the myoseptum (Li et al., 2004). CXCL12a is initially uniformly expressed along this stripe (Chitnis et al., 2012). Directed movement requires interaction of CXCL12a with CXCR4b and CXCR7b. CXCR4b is primarily expressed by leading (caudal) cells of the primordium during migration, while CXCR7b is primarily expressed by trailing (rostral) cells (Chitnis et al., 2012; Haas and Gilmour, 2006; Valentin et al., 2007). This polarized expression is believed to determine directed migration of the primordium, since the two receptors respond to CXCL12a in different ways. CXCR4b responds to CXCL12a with protrusive activity and directed migration (Luker et al., 2010). By contrast, when CXCL12a interacts with CXCR7b, no protrusions are observed, but CXCL12a is internalized and degraded (Chitnis et al., 2012). Although internalization of CXCL12a by either CXCR4b or CXCR7b results in intracellular degradation of CXCL12a, CXCR7b has a considerably higher binding affinity (Naumann et al., 2010). Thus, it is hypothesized that CXCR7b acts as a scavenger or sink for

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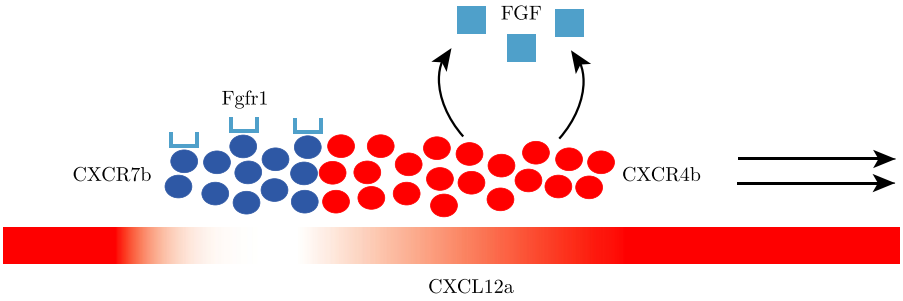

Fig. 1. Schematic of the factors that drive migration and cohesion of the primordium. Depletion of CXCL12a by trailing CXCR7b-expressing cells (blue) generates a local gradient of CXCL12a expression, which directs movement of leading CXCR4b-expressing cells (red). Trailing cells also express FGF receptor Fgfr1 and migrate toward FGF ligands secreted by leading cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CXCL12a, substantially depleting ligand levels at the trailing end of the primordium. A local gradient of ligand is then created, with lower levels of CXCL12a at the trailing end of the primordium.

Experiments by Dalle Nogare et al. (2014) have given us insight into the cooperation of primordial cells during migration. Via laser ablation, the primordium was separated into two fragments, a small leading fragment containing only CXCR4b-expressing cells and a larger trailing fragment primarily containing CXCR7b-expressing cells. The purpose of this experiment was to determine if depletion of CXCL12a by trailing cells could create a broad enough depression in CXCL12a activity to polarize migration of the separated leading fragment. The result in most trials was that the leading fragment stalled shortly after ablation, and then stretched, indicating that CXCL12a clearance by trailing CXCR7b-expressing cells cannot bias migration of the leading fragment over long distances. However, the trailing fragment, after initially stalling, always resumed caudal migration toward the leading fragment. Eventually, the two fragments rejoined, and the entire primordium migrated cohesively. This behavior of the trailing fragment was observed even after introducing the CXCL12a inhibitor chalcone-4-hydrate, which shows that migration of the trailing cells is not driven by a polarized response to CXCL12a. Further experiments showed that FGF ligands secreted by leading cells act as a chemoattractant for trailing cells (Fig. 1).

1.1. Goals of this work

Two previous models have been developed to describe cell cooperativity during migration of the primordium. Dalle Nogare et al. (2014) developed an agent-based computational model of primordium migration inspired by their experimental findings. This model successfully replicates the authors' laser ablation experiments. Knutsdottir et al. (2017) developed a 3D deformable ellipsoid mathematical model in which leading cells sense gradients of CXCL12a and trailing cells sense gradients of FGF. The authors investigated how cell division, adhesion, and chemotaxis affect primordium migration. They also challenged the model to replicate the results from Dalle Nogare et al. (2014), and found good agreement with experiments and the previous computational model. Although these models successfully reproduce experimental results, they do not address CXCL12a and FGF concentration profiles in detail and are not analytically tractable.

In this work, we formulate a simpler mathematical model to study a laser ablated zebrafish primordium. This model concentrates on primordium migration - we do not include cell proliferation or cell differentiation. We model the laser ablated portions of the primordium as two regions, a leading region that responds to CXCL12a activity and a trailing region that migrates towards FGFs secreted within the leading region. For certain parameter values, this model replicates experimental results. We fit parameters in our model to cell-tracking data obtained from a laser ablation video, thereby obtaining estimates for CXCL12a and FGF diffusion coefficients in the zebrafish lateral line system. For some parameter values, however, the leading region "runs away" from the trailing region, a behavior roughly akin to a neuromast deposition, but not seen in experiments or in previous models. We investigate this runaway case by deriving traveling wave solutions for CXCL12a and FGF and searching for parameter values that make a cohesive traveling wave solution impossible to obtain.

We begin by formulating the mathematical model, which consists of two partial differential equations (PDEs) for CXCL12a and FGF and two ordinary differential equations (ODEs) for rod positions as a function of time. We then discuss outcomes from simulations of the model and parameter fitting. Later, we derive traveling wave solutions for CXCL12a and FGF, as well as a self-consistency condition for velocity of the leading and trailing region. Finally, we use the traveling wave solutions we have obtained to investigate the self-consistency condition in more detail and discuss parameters that influence qualitative behavior of the model (runaway and cohesion).

2. The model

We model the primordium as two rigid rods, which represent the leading and trailing fragments created by Nogare et al. by laser ablation. This model is based on the following assumptions:

- CXCR4b and CXCR7b concentrations are constant in time.
- The expression domains for each receptor are distinct - the leading fragment expresses only CXCR4b and the trailing fragment expresses only CXCR7b.
- The leading and trailing fragments are the same length.
- Cells in each fragment internalize and degrade CXCL12a, with a tenfold higher degradation rate in the trailing CXCR7b-expressing fragment.
- Because primordium cells are flat and CXCL12a is expressed in a thin stripe, we reduce to one dimension. We model the boundaries of the domain as impermeable (no flux).

2.1. PDEs for ligands

Each rod has length $2l$; the leading rod has center of mass at c_1 and expresses only CXCR4b (R_4), while the trailing rod has center of mass at c_2 and expresses only CXCR7b (R_7). Within the bounds of the leading rod, CXCL12a is co-internalized and degraded by CXCR4b at a rate ρ_4. Within the trailing rod, CXCL12a is co-internalized and degraded by CXCR7b at rate ρ_7. CXCL12a is also secreted at a uniform rate in the entire domain $x \in [0, N]$. It also diffuses and undergoes natural decay. Thus, the equation for CXCL12a is

$$L_t = \alpha_L - \delta_L L - I(x - c_1)\rho_4 R_4 L - I(x - c_2)\rho_7 R_7 L + D_L L_{xx}, \qquad (1)$$