Moving in and Out: Dispersion of Cells in Self-Generated Gradients

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Abstract

Migrating cells can influence the direction of their own migration by metabolizing chemoattractants present in their environment. This is illustrated by the dispersal of melanoma cells, which break down lysophosphatidic acid and generate a gradient with increasing concentrations of lysophosphatidic acid distant from the tumor. Melanoma cells can then disperse away from the tumor as they migrate in the self-generated lysophosphatidic acid gradient. Thus, dispersal of tumor cells during invasion of the surrounding stroma might be driven by chemotaxis of cells along self-generated chemoattractant gradients.

Keywords: Self-generated gradient; Directed cell migration; Chemotaxis; Lysophosphatidic acid; LPA; Epidermal growth factor; EGF; Stromal derived factor-1; SDF-1

Introduction

Cell motility is necessary for organismic development, maintenance, and survival. The earliest form of directed cell migration was perhaps the migration of single cells towards nutrients [1], and evolved into the highly regulated directed cell migration observed in complex physiological contexts such as development and tissue repair in multicellular organisms. For example, directed migration is crucial for formation of fruiting bodies in the social amoeba Dictyostelium [2,3], and primordial germ cell migration in Drosophila, zebrafish, and mouse [4,5].

During directed migration cells are guided by chemoattractants or chemorepellents present in their environment. Repellent guidance, which leads to migration of cells away from a repellent guidance molecule, has been described mostly in the context of guidance of the nervous growth cone, where repellent guidance molecules include semaphorins, netrins and Slit [6-8]. Chemoattraction—the movement of cells towards a chemoattractant—is observed when cells converge to a steep gradient to be formed. As cells migrate away from the tumor the generated LPA gradient form a front which is followed by sparser, less defined clusters to become smaller as the cells disperse, resulting in lesser chemoattractant removal and shallower gradients, until cells come to a stop. These new cell colonies should start migrating again as tumor cells divide and the “satellite colonies” reach a size sufficient to reduce

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local chemoattractant levels and to generate a relevant gradient. Thus, invasion should occur in waves, where cells proliferate until a gradient sufficient to induce chemotaxis is built, disperse along the gradient until it collapses, and then increase colony size by proliferation until a critical mass is obtained that again allows formation of a self-generated gradient.

Third, self-generated gradients can, in principle, be sustained over long distances and long time periods. As it is the migrating cells themselves that build a gradient necessary for chemotaxis by decreasing the chemoattractant concentration present in the microenvironment, the cells should be able to maintain or re-establish the gradient indefinitely if (a) the chemoattractant is present in the environment and (b) the cells maintain their capacity to reduce the chemoattractant level in their vicinity. This is of importance as tumor cells invade and migrate far into the surrounding stroma in the course of weeks and months.

As cells migrate through the stroma, they may, however, also be exposed to and respond to local gradients of chemoattractants and chemorepellents. Thus, although tumor cells chemotaxing in a self-generated gradient should disperse in a centrifugal manner, the generation of complex self-generated gradients by tumor cell colonies of changing size and the migrating cells encountering other gradients may lead to more complex cell trajectories that result from the integration of multiple competing gradients or guidance cues a cell is exposed to [22]. The effect of the microenvironment and cellular context on the migratory phenotype can be illustrated by the response of melanoma cells to LPA. In the work described above, LPA signaling via LPA receptor 1 (LPA1) and degradation of LPA by tumor cells allows the cells to chemotax in a self-generated LPA gradient away from the tumor [19]. In contrast, LPA acts as a repellent guidance cue for mouse melanoma cells (B16) [23]. In this case, LPA mediates its effects via a different receptor, LPA5, to inhibit cell migration and to act as a chemorepellent [23]. Thus, LPA5-expressing melanoma cells would only disperse away from a tumor, if LPA levels in the tumor were higher than in the surrounding stroma. This complex regulation of effects of LPA, which depends on the capacity of cells as well as the cells’ environment to produce and remove LPA as well as the cells’ receptor expression profile, illustrates the complex regulation of directed migration by multilayered, non-redundant signaling networks such as the LPA signaling network [19,23-25].

In conclusion, self-generated gradients can be established by removal of chemoattractants from the microenvironment by degradation, uptake, or binding to decoy receptors. These self-generated gradients as they are observed in dispersing melanoma cells facilitate long-distance and long-term dispersal of cells through tissues as is observed during tumor cell invasion and possibly during reverse interstitial immune cell migration. However, these gradients and the response of cells to self-generated gradients might be modulated by other guidance cues existing in a cell’s environment.

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