Self-generated chemotactic gradients drive melanoma cell dispersal

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Keywords: *Chemotaxis, cancer metastasis, Lipid signaling, Lysophosphatidic acid*

Abstract

Melanoma is a particularly threatening cancer because cells spread rapidly and unusually early in tumour development. The melanoma literature contains a wide range of different stimuli which drive and steer cancer cell movement, but the fundamental reason that the cells are so invasive remains unclear.

We have developed an assay for melanoma cell steering based around full-view chemotaxis chambers. Surprisingly, cancer cells migrate directionally away from each other even in simple culture medium with no external stimuli. A detailed analysis of the mechanism of steering shows that chemotaxis towards an attractant, not other mechanisms such as chemorepulsion or contact guidance, is the key. The dominant attractant is LPA (lysophosphatidic acid), which is present at high levels in culture medium. LPA steers chemotaxis with unprecedented accuracy for cancer cells, and the lipid, its receptors and the enzymes that break it down are all necessary and sufficient for dispersal in several assays. In particular 3D organotypic models as well as 2D assays use self-generated LPA gradients. Cells rapidly break down LPA, yielding gradients that encourage individual cells to spread away from one another and into the surroundings.
We have also found gradients of LPA in real melanomas from mice in vivo, confirming the physiological importance of our results.

Generally, it is becoming increasingly clear that self-generated gradients are key steering mechanisms that underpin a wide range of biological and medical scenarios. We will discuss the reasons that self-generated gradients are important and why they are different from the more typically discussed gradients caused by external attractant sources.