Cells function as a ternary logic processor to decide their migration direction

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***Short Abstract* — Cells sense various environmental cues and process intracellular signals to decide their migration direction in many physiological and pathological processes. Although several signaling molecules have been identified in these directed migrations, it still remains elusive how cells decipher multiple cues, specifically chemical and fluidic cues. Here, we investigated the cellular signal processing machinery by reverse-engineering directed cell migration under integrated chemical and fluidic cues. We exposed controlled chemical and fluidic cues to cells using a microfluidic platform and analyzed the extracellular coupling of the cues with respect to the cellular detection limit. Then, the cell's migratory behavior was reverse-engineered to build the cell's intrinsic signal processing system as a logic gate. Our primary finding is that the cellular signal processing machinery functions as a ternary logic gate to decipher integrated chemical and fluidic cues. The proposed framework of the ternary logic gate suggests a systematic approach to understand how cells decode multiple cues to make decisions in migration.**

***Keywords* — cellular sensing and processing machinery, directed cell migration, systems biology**

I. Introduction

Directed cell migration is ubiquitous in many physiological and pathological processes [1-2]. During these processes, cells sense and process multiple and often heterogeneous cues, including chemical, mechanical, and fluidic ones [3-4]. Even though extensive research has been performed to identify key signaling molecules for various environmental cues [5-6], it is still puzzling how cells decipher simultaneous heterogenous cues and decide on a migration direction. Specifically, how cells respond to integrated chemical and fluidic cues is still not well understood. In the present study, we investigated the cellular signal processing machinery by reverse-engineering directed cell migration to elucidate a biophysical understanding of how cells decipher integrated chemical and fluidic cues to determine migration direction.

II. Results

A. The engineered microenvironment with controlled chemical and fluidic cues

We applied pressure-driven flow to the cells using microfluidic platform that were simultaneously exposed to the TGF-β gradient in two scenarios: 1) parallel flow of an additive cue with the TGF-β gradient and 2) counter flow of a competing cue to the TGF-β gradient. Then, we analyzed the complication of the integrated chemical and fluidic cues asking if the non-linear cue profiles fulfill the physical chemical cue-detection limit of the cells. In results, most of cells were located in the area where a relatively shallow gradient is present even for cells not to detect the gradient.

B. Intra-cellular processing of two cues simultaneously

We observed that cells effectively select a cue to follow in processing the mixed chemical and fluidic cues. When cells are capable of sensing both chemical and fluidic cues, cells tend to follow a chemical gradient direction in both the additive combination with the parallel flow and the competing with the counter flow. The cells were biased toward the upstream direction of the fluidic cue, only when the chemical gradient was too shallow for cells to detect it. Most strikingly, the cellular biased response was completely ruled out when the processing capacity is saturated with high background concentration of TGF-β.

C. Cellular signal processing machinery can be modeled as a ternary logic gate

By reverse-engineering the results, we construct a logic gate model to reconstitute the function of the cellular signal processing machinery. The cellular response to the cues of directions (+, 0, or –) presents three variables as outputs of cell migration direction, allowing us to develop a ternary logic system.

III. Conclusion

The present study laid a framework for understanding how cells decode chemical and fluidic cues to determine migration direction by proposing a ternary gate circuit.

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