Resolving the 'chemotactic wave paradox'

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Aggregation of *Dictyostelium* cells is dictated by chemotaxis towards traveling waves of cAMP that self-organize in the cell monolayer. Because reversal of spatial gradient occurs after every passage of wavefronts, it is unclear why the cells do not fall into a futile cycle of back and forth movement. This is the so-called 'chemotactic wave paradox'. By employing a microfluidics system, we have systematically analyzed chemotactic response towards traveling cAMP pulses of well-defined amplitude, duration and frequency. We found that the migratory direction depends on the wave speed. When the waves propagate fast (< 2min), cells come almost to a halt. For long stimulus duration (>10 min), cells reversed their migratory direction to trail the back of the wave. Cells migrate toward the direction of in-coming cAMP pulse when the stimulus duration is from 3 to 10 min, which is close to the period observed in aggregating field of *Dictyostelium*. These results indicate that cells are able to move towards the appropriate direction only when period of stimuli matches with characteristic time of cell response. We constructed theoretical models to analyze the observed behaviors, and found that the key feature required for directional migration is adaptive response to spatially homogeneous stimulus. It is well known that adaptive response underlies chemotaxis of bacterial cells to detect temporal changes in attractant concentration. Our present results suggest a new mechanism that combines temporal and spatial detection of signaling molecules.