Cell Sequence and Mitosis Affect Fibroblast Directional Decision-Making during Chemotaxis in Tissue-mimicking Microfluidic Mazes

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Directed fibroblast migration is central to highly proliferative processes in regenerative medicine and developmental biology, such as wound healing and embryogenesis. However, the mechanisms by which single fibroblasts affect each other’s directional decisions, while chemotaxing in microscopic tissue pores, are not well understood. Therefore, we explored the effects of two types of relevant social interactions on fibroblast platelet-derived growth factor-BB (PDGF-BB)-induced migration in microfluidic mazes: cell sequence and mitosis. Surprisingly, it was found that in both cases, the cells display behavior that is contradictory to the global chemoattractant gradient pre-established in the maze. In case of the sequence, the cells do not like to take the same path through the maze as their predecessor, when faced with a bifurcation. To the contrary, they tend to alternate - if a leading cell takes the shorter (steeper gradient) path, the cell following it chooses the longer (weaker gradient) path, and vice versa. Image-based modeling of the process shows that PDGF-BB consumption by the individual fibroblasts may be responsible for this phenomenon. Additionally, we found that when a mother cell divides, its two daughters go in opposite directions (even if it means migrating against the chemoattractant gradient and overcoming on-going cell traffic). Therefore, it is apparent that fibroblasts modify each other’s directional decisions in a manner that is counter-intuitive to what is expected from classical chemotaxis theory. Consequently, accounting for these effects could lead to a better understanding of tissue generation in vivo, and result in more advanced engineered tissue products in vitro.