Regulation of Rap1 signaling during Dictyostelium chemotaxis and development

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Concluding remarks

The movement in response to external chemical gradients is a phenomenon of widespread occurrence and an essential property of various organisms. This process is scientifically termed as chemotaxis. Bacterial, for example, relies on chemotaxis to find food (e.g. glucose) by swimming toward the highest concentration of food molecules. In multicellular organisms, chemotaxis is critical to early development (e.g. movement of sperm towards the egg during fertilization). Within the human body, the process of wound healing is guided by fibroblasts chemotaxis, as well as white blood cells home in on and engulf bacterial invaders. Importantly, metastasizing cancer cells subvert this process to migrate to and invade distant sites in a human body. Therefore, understanding how chemotaxis works may help us to understand how our immune system functions and also provides the necessary information to develop effective cures for a range of diseases, including cancer.

Mammalian neutrophils and the amoeba *Dictyostelium discoideum* are the most commonly used model systems to study eukaryotic chemotaxis. *Dictyostelium* is a species of soil-living amoeba that feeds on bacteria in its natural environment. When the food is scarce, individual *Dictyostelium* cells aggregate together, guided by the secreting of cAMP by themselves, to form fruiting body and spores, which enable them to survive in harsh conditions. Therefore, *Dictyostelium* serves an excellent model system to study chemotaxis.

Directional movement or chemotaxis is initiated by sensing of extracellular chemicals through transmembrane receptors that are located on the cell membrane, in case of *Dictyostelium* this are G-protein coupled receptors (GPCRs). These receptors then interact with downstream effectors to transmit and amplify the signals across the plasma membrane into the cytosol, where the "command" is performed through various cellular signaling pathways. In *Dictyostelium* there are minimal three components required for chemotaxis: GPCRs, heterotrimeric G proteins (Gα and Gβγ dimer), and small G-proteins of the Ras family. In this thesis, I particularly focused on a member of the Ras super family: Rap1.

Over the past two decades, Rap1 has been recognized world-wide to be an important regulator in a large variety of biological events, including chemotaxis. Despite substantial efforts,

the regulation of Rap1 in chemotaxis is still not completely understood. In this thesis, four Rap1 activators, GflB, RasGefL, RasGefQ, and GbpD, have been discovered and characterized. Our results indicate that chemotactic receptors recruits Rap1 activators, especially GflB, to the sides facing the highest amount of chemical waves called “leading edge”, which then communicates the signal received from receptors to locally assemble the crawling machinery that orients movement toward the source. Although some mechanisms are still not fully unraveled, our findings provide a milestone in the understanding how cells decide on the direction in which they need to migrate towards the extracellular chemical cues. We hope that our work enlightens and encourages new ideas and further investigations on understanding this process.