Identification of Ras activators (RasGEFs) triggering cellular amoeboid movement

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Abstract

Cells move around freely within our bodies. For instance, immune cells exhibit amoeboid movement, and it is known that this mechanism is shared with amoebas, which survive as single-celled organisms in nature. Consequently, research into cellular movement mechanisms is advancing by using the simple eukaryotic organism Dictyostelium discoideum, a cellular slime mould, as a model organism. Amoebae can initiate movement by determining their own direction, even in the absence of environmental stimuli that would prompt movement (Figure 1). However, the protein responsible for this spontaneous directional decision-making remained unclear. Our research has revealed that direction is determined and cell movement occurs when the activator RasGEFX acts on Ras, a small G protein, leading to localized activation of Ras on the cell membrane (Figure 2).

Background & Results

Amoeboid movement is driven by the formation of pseudopodia at the front of the cell. This process is regulated by the Ras pathway within the cell's signaling system. Where activated Ras accumulates on the cell membrane determines the location of the cell's front (Figure 1). Even when cell deformation and movement are suppressed in a constant, uniform environment, this region naturally emerges and propagates as travelling waves along the cell membrane. This demonstrates that Ras activation and inactivation occur cooperatively in a spatiotemporal manner on the cell membrane. This is a form of self-organization, suggesting the involvement of an excitable molecular reaction network. However, the diversity of Ras activators (RasGEFs) in cellular slime moulds, which comprise 25 types with different nucleotide sequences, makes identifying the excitable network and elucidating the mechanism difficult.

We created genetically engineered cell lines that overexpressed each RasGEF gene individually, and analyzed the dynamics of activated Ras. By focusing on the temporal and spatial characteristics of the travelling wave and performing statistical analyses, we revealed that RasGEFX is necessary to initiate the accumulation of activated Ras (Figure 2). Indeed, cells with higher RasGEFX expression exhibited a higher frequency of regions enriched with activated Ras, resulting in more frequent pseudopod formation during cell migration. Furthermore, we found that three other RasGEFs also contribute to Ras activation, each playing a distinct role alongside RasGEFX in controlling spontaneous cell migration. Specifically, we found that higher RasGEFB expression levels correlate with larger activated Ras-enriched regions and larger pseudopodia. Thus, it became clear that the cell's amoeboid movement is achieved through RasGEFX, an essential component of the excitable system that determines its temporal characteristics, and through RasGEFB, which controls its spatial dynamics.

Significance of the research and Future perspective

The findings of this study are significant because they help to explain the fundamental principles of spontaneous cellular behavior. This research may eventually lead to methods for controlling cell movement within the body.

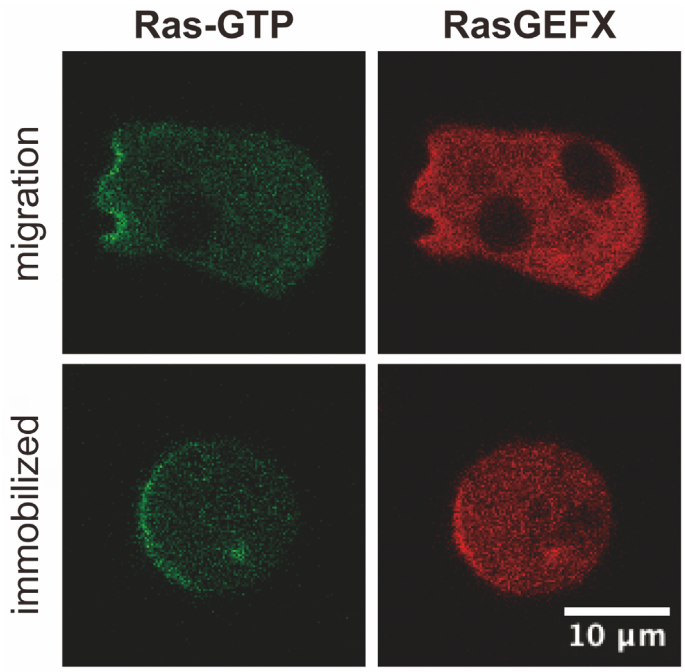

Figure 1. RasGEFX triggers self-organization of cellular polarity

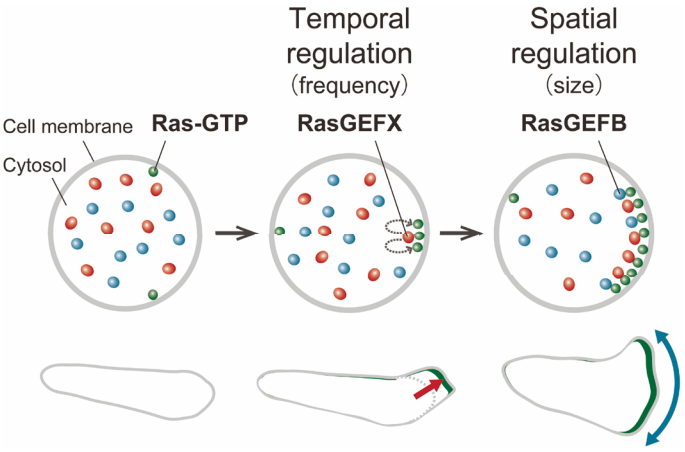

Figure 2. Task division by genetically distinct RasGEFs

Patent

Treatise Iwamoto, Koji; Matsuoka, Satomi; Ueda, Masahiro. Excitable Ras dynamics-based screens reveal RasGEFX is required for macropinocytosis and random cell migration. Nature Communications. 2025, 16, 117. doi: 10.1038/s41467-024-55389-2
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