論文内容の要旨

論文題目

Frequency Response Analysis of Akt Signal Transduction Pathway
(Akt シグナル伝達経路の周波数応答解析)

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In cellular signal transduction, information is encoded as temporal patterns of signaling molecules and is selectively transmitted and decoded by characteristics of the signal transduction pathways, leading to specific cellular responses. The Akt pathway plays evolutionary conserved roles in cell survival, growth and proliferation in response to growth factors. By recent advancements of molecular biology, knowledge about molecules which constitute the Akt pathway and its interactions is growing. However, dynamics and characteristics of signal propagation in the pathway, in other words, temporal activation patterns of molecules and their regulation mechanisms remain elusive.

Signal processing in the Akt pathway have been examined in this thesis by quantitative measurements of signaling dynamics, modeling, simulation, and employing frequency response analysis. Distinct dose-responses of S6 phosphorylation were experimentally found in PC12 cells in response to nerve growth factor (NGF) and epidermal growth factor (EGF). I also obtained counter-intuitive results indicating that the peak amplitudes of receptor and downstream phosphorylation are decoupled; weak sustained EGF receptor phosphorylation, rather than strong transient phosphorylation, strongly induced S6 phosphorylation, a downstream molecule of Akt. A developed phenomenological simulation model of the Akt pathway successfully reproduced the NGF- and EGF-induced dynamics observed in the experiment. In frequency response analysis, amplitude spectra were obtained by mapping the time courses of the model

into frequency domain with Fourier transform, and the signal transfer efficiency was examined by using the ratio of downstream and upstream amplitude spectra. Using a frequency response analysis, I found that the Akt pathway exhibits a low-pass filter characteristic and that this characteristic of the Akt pathway can explain the convex dose response of S6 phosphorylation and decoupling effect of the peak amplitudes between receptor and downstream phosphorylation. Furthermore, I found that lapatinib, an EGFR inhibitor used as an anti-cancer drug, converted strong transient Akt phosphorylation into weak sustained Akt phosphorylation, leading to an even stronger S6 phosphorylation than in the absence of the inhibitor because of the low-pass filter characteristic of the Akt pathway. This indicates that the EGFR inhibitor can be a potential downstream activator. Because the low-pass filter characteristic is an intrinsic feature of biochemical reactions, our findings raise a caution in interpreting biological and pharmacological data without temporal information.