論文の内容の要旨

論文題目

Systems biology analysis of temporal pattern transfer in signal transduction mechanisms

（シグナル伝達機構における時間パターン伝播の
システム生物学的解析）

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Cells use signal transduction to respond the external stimuli and exert biological functions. Cells should detect strength of a stimulus and accordingly regulate responses. By recent advancement of molecular biology, qualitative knowledge of the components of the signal transduction systems has been growing. However, the quantitative input-output relationships of cell response and their regulation mechanisms remain elusive. Especially, how efficiency of signal transfer and sensitivity of a signaling pathway to strength of an activator or an inhibitor are controlled is a fundamental unsolved question.

In our previous work about Akt pathway, we found counterintuitive results that peak amplitudes of receptor and downstream signals are decoupled; a weak sustained receptor signal, rather than a strong transient signal, strongly induced downstream response. By experiments and simulations, we found that the low-pass filter characteristics of the Akt pathway can explain the decoupling effect. This indicates that, depending on temporal patterns, transfer efficiency of the peak amplitude is variable, and consequently the sensitivity of peak amplitude is also variable.

Here, we examined the signal transfer efficiency of the peak amplitude in a simple signaling pathway that can be approximated by a consecutive first-order reaction, which exhibits low-pass filter characteristics. We theoretically found that signal transfer efficiency attenuates when the time constant of the negative regulation of the downstream molecule is longer than the duration of transient peak of the upstream molecule. We experimentally found that the quantitative property of the attenuation of the signal transfer efficiency was conserved among species of signaling pathways including Akt and ERK pathways, growth factors and cell lines.

Because of this property, the effective dose of the activator for the downstream molecule becomes smaller than that for the upstream molecule, indicating an increased sensitivity of the downstream molecule to the activator. This increase became larger when the negative regulation became weaker. Similarly, the effective dose of an inhibitor for the downstream molecule becomes larger than that for the upstream molecule, indicating a decreased sensitivity of the downstream

molecule to the inhibitor. This decrease became larger when the negative regulation became weaker. We experimentally verified the sensitivity decrease to an inhibitor using the lapatinib (an EGF receptor inhibitor)-dependent inhibition of Akt and S6 phosphorylation.

These results demonstrate that attenuation of signal transfer efficiency through negative regulation is a novel conserved property of the signaling pathway. These results also suggest that cells can control their sensitivity to an activator and inhibitor by changing the expression levels of negative regulators, such as phosphatase or protease.

<Summary figure>