論文の内容の要旨

論文題目

Temporal Decoding of MAP Kinase and CREB Phosphorylation by Selective Immediate Early Gene Expression

（MAP キナーゼ経路による初期応答遺伝子発現誘導機構のシステム生物学的解析）

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A wide range of growth factors encode information into specific temporal patterns and combinations of phosphorylation of signalling molecules, that are decoded by limited numbers of downstream immediate early gene products (IEGs) expression. However, how such limited numbers of IEGs selectively decodes a wide range of upstream information remains unknown. Here we show that the IEGs selectively decode the temporal patterns and combinations of upstream signals via distinct temporal filters characteristics and switch-like dose-dependency. Based on the concept of system identification, we measured 10,000 points of time series of phosphorylation of MAPKs (ERK, JNK, p38) and

CREB, and protein expression of the IEGs (c-FOS, c-JUN, EGR1, FOSB, JUNB), and developed a nonlinear autoregressive exogenous (ARX) model, one of the statistical data-driven models. We found that each IEG shows distinct temporal and dose-dependency on upstream signals, indicating a high performance in decoding of upstream signals. Pulsatile stimulation of NGF induced pulsatile ERK phosphorylation, selectively inducing EGR1 expression rather than c-FOS and c-JUN expression, that is mediated by distinct temporal filter characteristics. Conjunctive stimulation of NGF and PACAP induced synergistic JUNB expression, indicating that JUNB serves as conjunctive detector of NGF and PACAP. Selective decoding of conjunction of growth factors by JUNB was mediated by a switch-like dose response of JUNB to c-FOS. Thus, specific temporal patterns and combinations of MAPKs and CREB phosphorylation that encode information of a wide range of growth factors are selectively decoded by the IEGs expressions via distinct temporal filter characteristics and switch-like response.