Brief Communication

Why have serine/threonine/tyrosine kinases been evolutionarily selected in eukaryotic signaling cascades?

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ABSTRACT

The signal transduction systems of eukaryotes are different from those of prokaryotes with respect to their structures and mechanisms. The main signal transduction system of prokaryotes called the two-component system (TCS) is a one-step phosphorelay system composed of a histidine kinase (HK) while the central signal transduction system of eukaryotes called the mitogen-activated protein kinase (MAPK) cascade system (MCS) is a multi-step phosphorelay system composed of serine/threonine/tyrosine kinases (STYKs). The two signal transduction systems are also different in their transphosphorylation mechanisms. HK in the TCS transfers its own phosphate group to the response regulator protein while STYKs in the MCS phosphorylate other proteins using ATP. We were intrigued by the different dynamics resulting from such differences and wondered why STYKs instead of HKs have been evolutionarily selected in eukaryotic signaling cascades. In this paper, we compared the dynamical characteristics of two mathematical models which reflect such differences between the TCS and the MCS, and found that STYKs are more appropriate for cascade structures in eukaryotic signal transduction than HK with respect to the duration and settling time of response signals.

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1. Introduction

Living organisms have developed different signal transduction systems to react to their environmental changes. For instance, in prokaryotes, the two-component system (TCS) composed of a histidine kinase (HK) and a response regulator protein (Fig. 1A) is the main signal transduction system. HK is a multi-functional enzyme which has autokinase, phosphotransfer, and phosphatase activities (Marina et al., 2005). In the TCS, the autophosphorylated HK which is the activated form of HK transfers its own phosphoryl group to the response regulator protein, and the phosphorylated response regulator protein regulates the transcription of specific target genes (Chang and Stewart, 1998; Stock et al., 2000; Wurgler-Murphy and Saito, 1997). Different from prokaryotes, in eukaryotes, the mitogen-activated protein kinase (MAPK) cascade system (MCS) composed of three kinases (MAPK kinase kinase (MAPKKK), MAPK kinase (MAPKK), and MAPK) is the most common signal transduction system. An activated (phosphorylated) MAPKKK activates MAPKKs by phosphorylating two conserved serine residues, and then the activated MAPKK activates MAPKs by phosphorylating the conserved threonine and tyrosine residues (Fig. 1B). Finally, the activated MAPK phosphorylates and regulates several cellular proteins and nuclear transcription factors (Huang and Ferrell, 1996; Kolch, 2000; Schoeberl et al., 2002; Wurgler-Murphy and Saito, 1997; Yoon and Seger, 2006; Zhang and Liu, 2002).

As aforementioned, the TCS and the MCS have different structures and mechanisms. The TCS uses only one kinase (HK) to transfer signals while the MCS uses serine/threonine/tyrosine kinases (STYKs). In addition, HK transfers its own phosphate group to the response regulator protein while STYK phosphorylates other proteins using ATP. From these differences, we find that the TCS can more quickly respond to a stimulus than the MCS, and such a quick response of the TCS in prokaryotes is generally advantageous for their survival. We note however that the quick response is not always advantageous since a system may also respond to fake signals such as short-term noises. Therefore, a slow response of the MCS can help enhance the robustness of a system to noises. In addition, it is well known that the cascade of the MCS induces
ramification or amplification of signals (Chang and Karin, 2001; Huang and Ferrell, 1996; Seger and Krebs, 1995). These characteristics of the MCS are the reasons why eukaryotic signaling systems have been evolved into cascade structures such as the MCS. Here, the question is why eukaryotes have evolutionarily selected STYKs instead of HKs in MCS. To address this question, we constructed mathematical models of signal transduction systems reflecting the differences between HKs and STYKs. From computational experiments, we found that STYKs are more appropriate for signaling cascades than HK with respect to the duration and settling time of response signals.

2. Materials and Methods

We built mathematical models for signal transduction systems composed of HKs and those composed of STYKs, respectively. Our goal was to unravel the dynamical differences between HK cascade and STYK cascade. So, we did not attempt to construct mathematical models that realize every single detail of real systems, but focused on constructing simplified mathematical models that can capture the essential properties. For the HK cascade model (see Table S1 in Supplementary Material), we constructed it such that it has the same cascade structure with STYK cascade for proper comparison. For the STYK cascade model (see Table S2 in Supplementary Material), we basically simplified the Schoeberl model (Schoeberl et al., 2002) by removing the feedback loops in order to focus on the three-layer cascade. The mathematical models based on the transphosphorylation of HK type (see Tables S3 and S4 in Supplementary Material) and the mathematical models based on the transphosphorylation of STYK type (see Tables S5 and S6 in Supplementary Material) were constructed with different phosphate sources. In other words, HK uses its own phosphate to phosphorylate its substrates while STYK uses ATP as a phosphate source to phosphorylate its substrates. Any further details on each mathematical model can be found in Supplementary Material.

3. Results

The activation of C domain in HK is 10-fold faster than the phosphorylation of H domain (Levit et al., 1996) and the autophosphorylation rate is similar to the dephosphorylation rate (Surette et al., 1996). Moreover, the autophosphorylation of HK is 20-fold faster than the transphosphorylation (Wolfe et al., 1994). In the case of STYK, the activation rate of Ras and the phosphorylation rate of MEK (MAPKK) are similar and the phosphorylation of MEK (MAPKK) is 10-fold faster than the phosphorylation of Raf (MAPKKK) (Schoeberl et al., 2002). Taking account of the different phosphorylation rates of kinases, we constructed simplified mathematical models of the TCS and the MCS. In this case, we assumed that the phosphorylation rates are much larger than the dephosphorylation rates since we are focusing on the roles of kinases although the phosphatase activity is also an important factor determining the duration of signaling (Heinrich et al., 2002). As we focus on the dynamics of the cascades, we excluded the feedback loops in the mathematical models (see Section 2 and Supplementary Material). Fig. 2 shows the stimulus–response curves of the two models. From Fig. 2, we found that the Hill coefficient of the MCS response curve (Fig. 2B) is larger than that of the TCS response curve (Fig. 2A). This implies that the MCS is more sensitive to stimuli than the TCS. It has been known that the signaling cascades can induce signal amplification and ultrasensitivity (Huang and Ferrell, 1996), and we confirmed it again through this simulation result. Fig. 3A and B shows the temporal response curves for a step-stimulation. We found that the TCS promptly reacts for any stimuli while the MCS promptly reacts only for strong stimuli. Moreover, the MCS maintains the response for a longer period of time after the stimulation disappears than the TCS does (see Supplementary Material). To confirm the robustness of computational experiments, we have repeated the simulations of the TCS model (HK cascade model) for a wide range of parameter values obtained by global rescaling (i.e., 10^{-3} to 10^{3} folds) of the nominal parameter values in Table S1 of Supplementary Material. All the simulation results were similar to that of Fig. 3A. In the case of the MCS model, we also found that the duration of the response signal after removing...
stimulation increases as the stimulation signal gets increased (see Fig. 3B).

On the other hand, we note that the transphosphorylation mechanisms of HKs and STYKs are also different with respect to their phosphate sources. A phosphorylated HK transfers its own phosphate group to a response regulator while a phosphorylated STYK phosphorylates other kinases by using ATPs. To compare the dynamical characteristics of two phosphorylation mechanisms, we built mathematical models of two kinds of two-component systems (composed of a sensor kinase A and a response regulator B) having two transphosphorylation mechanisms (see Supplementary Material). Fig. 4A shows the settling time (i.e., the time taken to reach a steady state) with respect to the ratio \( B_0/A_0 \) where \( A_0 \) and \( B_0 \) denote the total amounts of the proteins A and B, respectively, by setting \( A_0 = 1 \). From Fig. 4A, we found that the two-component system composed of HK arrives at its steady state faster than the two-component system composed of STYK. In other words, the transphosphorylation mechanism of HK is more efficient for signaling than that of STYK in the case of the two-component system.

In order to study the three-component (i.e., signaling cascade) case, we constructed two mathematical models of signaling cascades composed of three components (A, B and C) with two transphosphorylation mechanisms. Fig. 4B shows the simulation result where we assumed that the total amounts of B and C are same (\( B_0 = C_0 \)). Note that the signaling cascade composed of HKs arrives at its steady state faster for a small ratio of \( B_0/A_0 \) while the signaling cascade composed of STYKs arrives at its steady state faster for a large ratio of \( B_0/A_0 \). Hence, for a large ratio of \( B_0/A_0 \), the transphosphorylation mechanism of STYKs is more efficient with respect to settling time in signaling cascades than that of HKs.

4. Discussion

In prokaryotes, a stimulus signal recognized by HK in a TCS is directly transferred to its target genes through the cognate RR of HK in the cytosol (Fig. 1A) while eukaryotes transfer extracellular stimuli to the target genes through multi-step signaling processes which also require a nuclear transport (Fig. 1B). Since the nuclear transport is controlled by complex mechanisms, it would be more efficient to reduce the number of occurrences of the nuclear transport by minimizing the number of signaling molecules to enter the nucleus in signaling cascades. In this respect, eukaryotes might have evolved to integrate signal transduction pathways as follows: in MAPK/ERK pathway, several kinds of stimuli can activate ERKs in the cytosol, and the activated ERKs enter the nucleus in order to activate the stimulus-specific transcription factors (Helmbrecht et al., 2000; Li and Qian, 2003). Here, as ERK regulates the transcription factors related to both proliferation and differentiation in the cell cycle regulation, there should be a mechanism for ERK to choose whether to proliferate or differentiate. The most convincing hypothesis regarding such mechanism is that the decision depends on the duration of ERK activation. A short duration of ERK activation induces proliferation while a long duration of ERK activation induces a growth arrest and leads to the differentiation (Helmbrecht et al., 2000). Besides the cell cycle regulation, the duration of ERK activation is important to the synaptic plasticity (Thomas and Huganir, 2004). Therefore, regulating the duration of
a response signal is essential in the signal transduction system of eukaryotes. Our simulation results show that the MCS can more efficiently regulate the duration of a response signal than the TCS can do (Fig. 3).

Signal transduction systems need to transfer proper signals as fast as possible to quickly respond to environmental changes. While the transphosphorylation mechanism of HK in the TCS is faster in signaling than that of STYK, the transphosphorylation mechanism of STYK transfers signals faster than that of HK in the case of signaling cascades (Fig. 4). This might be another reason why STYKs are primarily chosen for eukaryotic signal transduction cascades.

We have explored the dynamical characteristics of TCSs and MCSs through mathematical modeling and simulations, and found some reasons why MCSs with STYKs are used as signal transduction systems in eukaryotes. First, MCSs can more efficiently regulate the duration of a response signal than TCSs can do. Such efficient regulation of duration is essential in eukaryotes. For instance, in MAPK/ERK pathway, ERK which transfers different signals from several stimuli can accurately activate the stimulus-specific gene as fast as possible to quickly respond to environmental changes. While the transphosphorylation mechanism of HK in the TCS is faster in signaling than that of STYK, the transphosphorylation mechanism of STYK transfers signals faster than that of HK in the case of signaling cascades (Fig. 4). This might be another reason why STYKs are primarily chosen for eukaryotic signal transduction cascades.

Finally, we conclude that these advantages of STYK over HK made eukaryotes evolutionarily select STYKs for their signaling cascades.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.compbiolchem.2008.02.005.

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