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Scaffold-mediated nucleation of protein signaling complexes: Elementary principles

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ABSTRACT

Proteins with multiple binding sites play important roles in cell signaling systems by nucleating protein complexes in which, for example, enzymes and substrates are co-localized. Proteins that specialize in this function are called by a variety names, including adapter, linker and scaffold. Scaffold-mediated nucleation of protein complexes can be either constitutive or induced. Induced nucleation is commonly mediated by a docking site on a scaffold that is activated by phosphorylation. Here, by considering minimalist mathematical models, which recapitulate scaffold effects seen in more mechanistically detailed models, we obtain analytical and numerical results that provide insights into scaffold function. These results elucidate how recruitment of a pair of ligands to a scaffold depends on the concentrations of the ligands, on the binding constants for ligand–scaffold interactions, on binding cooperativity, and on the milieu of the scaffold, as ligand recruitment is affected by competitive ligands and decoy receptors. For the case of a bivalent scaffold, we obtain an expression for the unique scaffold concentration that maximally recruits a pair of monovalent ligands. Through simulations, we demonstrate that a bivalent scaffold can nucleate distinct sets of ligands to equivalent extents when the scaffold is present at different concentrations. Thus, the function of a scaffold can potentially change qualitatively with a change in copy number. We also demonstrate how a scaffold can change the catalytic efficiency of an enzyme and the sensitivity of the rate of reaction to substrate concentration. The results presented here should be useful for understanding scaffold function and for engineering scaffolds to have desired properties.

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1. Introduction

Proteins involved in cell signaling typically possess multiple binding sites, and as a result, a common feature of these proteins is their ability to interact with several binding partners to form heterogeneous protein complexes [1]. Some proteins specialize in the nucleation of protein complexes [2]. For example, Ste5 is a well-studied scaffold protein that acts in a yeast MAP kinase cascade; it binds all three kinases of the cascade, Ste11, Ste7, and Fus3 [3]. The interaction of Fus3 with Ste5 is modulated by multisite phosphorylation of Ste5 [4]. One function of Ste5 is to co-localize enzyme–substrate pairs (e.g., Ste11 and Ste7) in the cascade [5], which contributes to switch-like cellular responses to signals [4]. Two well-known examples of scaffold-like proteins that nucleate protein complexes in mammalian signaling systems are the Grb2 adapter protein in the epidermal growth factor receptor (EGFR) pathway [6] and the LAT linker protein in the T cell receptor (TCR) pathway [7–9]. The binding sites in LAT are activated by tyrosine phosphorylation, and as a result, the valence of LAT and the abundance of functional LAT binding sites can be quickly changed by changes in kinase and phosphatase activities, with these changes serving to modulate the effect of LAT on signaling [10]. In addition to proteins with dedicated scaffold functions, proteins that have catalytic activities and protein complexes, such as ligand-induced receptor dimers, can also function as scaffolds, i.e., take on the function of facilitating the formation of multicomponent complexes through multivalent binding.

Many functions have been ascribed to scaffold proteins [2,9,11–14]. For example, scaffolds have been suggested to control the specificities of enzymes, coordinate spatiotemporal aspects of signaling, and amplify or attenuate signals. To better understand the mechanisms by which scaffolds influence cell signaling, researchers have formulated mathematical models to study the effects of scaffolds on specific signaling systems and to study the generic properties of scaffolds [15–21,4,22]. The ability of a scaffold to either amplify or attenuate signaling was demonstrated by Levchenko et al. [16] using a mathematical model for a MAP kinase cascade. In this model, scaffold enhancement of signaling results from scaffold-mediated nucleation of an enzyme with its substrate, whereas scaffold inhibition of signaling results from excess

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scaffold, which separates enzyme and substrate into distinct enzyme-scaffold and substrate-scaffold complexes. This effect is equivalent to the well-known prozone effect in antibody-antigen reactions [15]. Heinrich et al. [17] further studied these effects of scaffolds on protein kinase cascades. More recently, Locasale et al. [20] studied how scaffolds affect competition between phosphatases and kinases, finding that scaffolds can have positive and negative effects on signaling for reasons related to the kinetics of signaling events.

Modeling has improved our understanding of scaffold function, but many of the reported modeling studies of scaffold function have been based solely on simulations, which makes the results dependent on the parameter values considered in simulations. In addition, many of the models used to study scaffolds incorporate mechanistic details that are likely to be extraneous for understanding scaffold function broadly. Greater theoretical understanding of the design principles of scaffolds could perhaps be obtained by focusing on minimalist models that are relatively easy to analyze. With a better understanding of scaffold design principles, we can hope to manipulate scaffold function through precise tuning of scaffold and system properties. Manipulating the properties of a scaffold or its milieu to alter the behavior of a cell signaling system is known to be feasible [5,23,24]. For example, Lim and co-workers have demonstrated that the response of a cell to a signal can be changed qualitatively by altering the binding specificities of a scaffold [5].

Here, by considering minimalist models for multivalent scaffold–ligand interaction, we investigate the recruitment of ligands to a scaffold and the effects of a scaffold on an enzymatic reaction. We obtain a number of analytical and numerical results, mostly for a model that characterizes the equilibrium formation of a ternary complex composed of a scaffold and two binding partners. In this ternary-complex model, the scaffold is bivalent and its monovalent binding partners are taken to be an enzyme–substrate pair. Each binding partner, or ligand, interacts with one of the two binding sites of the scaffold. We evaluate the relevance of the ternary-complex model through comparisons with more mechanistically detailed models for cell signaling systems that involve scaffolds. The ternary-complex model is similar in mathematical form to a variety of models that have been used to study receptor signaling [25,26] and multivalent ligand–receptor binding [27–29].

The remainder of this report is organized as follows. In Section 2, we introduce models and present analytical results relevant for understanding the effects of scaffold valence, negative and positive cooperativity in binding of multiple ligands to a scaffold, competitive inhibitors of ligand–scaffold interactions, and decoy receptors. We also develop an approximate rate law for scaffold-mediated enzyme kinetics. Our most significant analytical result is a design equation that characterizes how the scaffold concentration that maximally nucleates a ternary complex depends on equilibrium binding constants and ligand concentrations. Interestingly, this scaffold concentration is independent of cooperativity in ligand binding. In Section 3, we present numerical results that complement the analytical results. The numerical results include a demonstration that our simple ternary-complex model recapitulates scaffold effects seen in more mechanistically detailed models and a demonstration that a single scaffold can nucleate distinct signaling complexes at different scaffold concentrations. We conclude with a brief discussion (Section 4).

2. Models and analytical results

The models that we will consider are illustrated in Fig. 1 and described below, along with various analytical results relevant for understanding scaffold function.

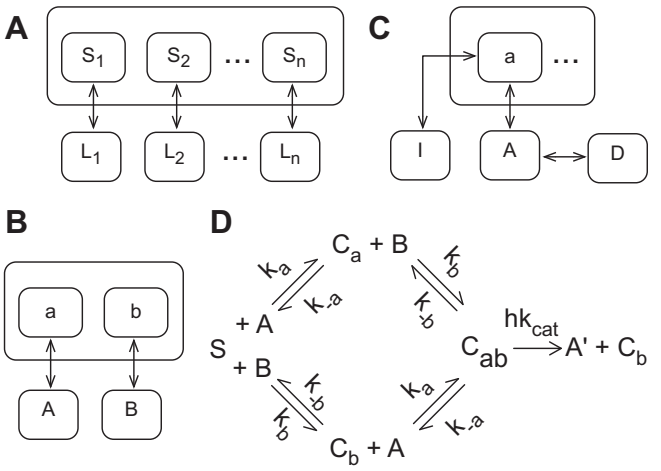

Fig. 1. Minimalist models for ligand–scaffold interactions. (A) A scaffold with n sites ($S_1,\ldots,S_n$). Each site S_i interacts with a distinct ligand L_i. (B) Ternary-complex model. A bivalent scaffold with sites a and b interacts with monovalent ligands A and B, respectively. (C) A scaffold site a interacts with a ligand A and a competitive inhibitor I. The ligand A interacts with a decoy receptor D. (D) A reaction scheme for a scaffold-mediated enzymatic reaction that produces a product A'. The substrate is scaffold ligand A and the enzyme is scaffold ligand B. See text for discussion.

2.1. Multivalent scaffold with independent binding sites

We consider a scaffold protein with $n \geqslant 2$ binding sites. Each scaffold binding site i interacts independently with a distinct monovalent ligand i, as illustrated in Fig. 1(A). Thus, we consider the following reactions:

$$S_i + L_i \rightleftharpoons B_i, \quad i = 1,\ldots,n, \tag{1}$$

where S_i represents free site i, L_i represents free ligand i, and B_i represents bound site i (or equivalently, bound ligand i). Using the same symbols for chemical species in Eq. (1) for the corresponding concentrations, we can write the following equilibrium relations, which are derived from the law of mass action:

$$K_i B_i = S_i L_i, \quad i = 1,\ldots,n, \tag{2}$$

where K_i is an equilibrium dissociation constant. Assuming conservation of mass, such that $S_0 = S_i + B_i$ and $L_{i_0} = L_i + B_i$, where S_0 is the total concentration of scaffold protein and L_{i_0} is the total concentration of ligand i, we find from Eq. (2) that

$$B_i^2 - (S_0 + L_{i_0} + K_i)B_i + S_0 L_{i_0} = 0. \tag{3}$$

From the quadratic formula and the physical constraint that $B_i < \min(L_{i_0}, S_0)$, it further follows that

$$B_i = \frac{S_0 + L_{i_0} + K_i - \sqrt{(S_0 + L_{i_0} + K_i)^2 - 4S_0 L_{i_0}}}{2}. \tag{4}$$

This equation and the mass conservation relations given above can be used to completely determine the equilibrium state of the system described in Fig. 1(A).

We will now show that there is a unique scaffold concentration S_0^{opt} that maximizes C_n, the equilibrium concentration of scaffold protein with all n sites occupied. The analytical results that follow complement numerical results obtained in earlier modeling studies of scaffold function [11,15–17].

We note that the equilibrium quantity B_i/S_0 can be interpreted as the probability that scaffold binding site i is occupied at equilibrium. Likewise, C_n/S_0 can be interpreted as the joint probability that all n scaffold binding sites are occupied. Thus, because each scaffold binding site is assumed to interact with its cognate ligand independently, we can write

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