Short Commentary   ⓐ Open Acess

Dynamics of Scaffolding Proteins

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Scaffolding proteins have critical roles in cellular signaling pathways in which they bring multiple binding partners together to facilitate their concerted interactions and functions. They achieve this by being composed of several protein–protein interaction modules, most notably PDZ (postsynaptic density 95/discs large/zona occludens-1) and SH3 (Src homology 3) domains. Additionally, scaffolding proteins and their partners generally show highly specific subcellular localizations. Some well-studied examples include MAPK signaling during mating in the budding yeast using the scaffold Ste5p, neuronal synaptic signaling exploiting PSD-95, and photosensory reception in Drosophila signaling using InaD (inactivation no after-potential D. Other scaffolds, such as members of the NHERF (Na+-H+ exchanger regulatory factor) family and SNX27 (sorting nexin family member 27), are involved in the stabilization, sorting, recycling, and localization of cell surface receptors.

Scaffolds also perform critical roles in cell polarity. The scaffold Bem1 coordinates a feedback loop to generate localized activation of Cdc42 to ensure that budding yeast assembles a single bud. The PDZ scaffolds par-3 and par-6 are essential for establishment of asymmetry and proper cleavage in the early embryo of Caenorhabditis elegans . In Drosophila, Scrib (scribble), Dlg (discs large), Baz (Bazooka), and Sdt (stardust) are all PDZ scaffolds that regulate epithelial polarity. Another PDZ scaffold, ZO-1 (zona occludens-1) is involved in the stabilization and barrier function of tight junctions. Additionally, the linking proteins α- and β-catenin play vital roles in cadherin-based cell–cell adhesion, which helps give rise to the functional organization of cells into tissues. The overwhelming majority of these scaffolds involved in polarity are highly conserved across species, further highlighting their importance.

The name "scaffold" implies the formation of a stable complex, a notion further reinforced by their highly specific localizations. However, over the past decade, there have been examples of scaffolding protein complexes long thought to provide stable linkages but subsequently found to be surprisingly dynamic. These advances have been driven by the increased accessibility of techniques such as FRAP (fluorescence recovery after photobleaching) and photoactivation to examine the dynamics of components in vivo. Despite these advances, the in vivo dynamics of many scaffold complexes are often not considered. In this Perspective, we aim to draw attention to this phenomenon by discussing some examples of unexpectedly dynamic scaffold complexes and to discuss how this may relate to their physiological roles. Further, we wish to encourage more analyses of in vivo dynamics of cellular components, as unexpected insights can emerge. Finally, we explore the issue that dynamic protein complexes are likely systematically underrepresented in current proteomic data.

The terms dynamic and stable serve as qualitative descriptors of the dynamics of components in the context of the stability of the structures in which they participate. The affinity of protein–protein interactions is a function of their on and off rates. On rates are largely limited by diffusion (on the order of 10^6 to 10^7 $M^{-1}s^{-1}$), so the off rate is often the determining factor of binding affinity. Techniques such as FRAP measure the off rate of proteins based on their fluorescence recoveryrates.