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Dynamic multiprotein assemblies shape the spatial structure of cell signaling

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ABSTRACT

Cell signaling underlies critical cellular decisions. Coordination, efficiency as well as fail-safe mechanisms are key elements. How the cell ensures that these hallmarks are at play are important questions. Cell signaling is often viewed as taking place through discrete and cross-talking pathways; oftentimes these are modularized to emphasize distinct functions. While simple, convenient and clear, such models largely neglect the spatial structure of cell signaling; they also convey inter-modular (or inter-protein) spatial separation that may not exist. Here our thesis is that cell signaling is shaped by a network of multiprotein assemblies. While pre-organized, the assemblies and network are loose and dynamic. They contain transiently-associated multiprotein complexes which are often mediated by scaffolding proteins. They are also typically anchored in the membrane, and their continuum may span the cell. IQGAP1 scaffolding protein which binds proteins including Raf, calmodulin, Mek, Erk, actin, and tens more, with actin shaping B-cell (and likely other) membrane-anchored nanoclusters and allosterically polymerizing in dynamic cytoskeleton formation, and Raf anchoring in the membrane along with Ras, provides a striking example. The multivalent network of dynamic proteins and lipids, with specific interactions forming and breaking, can be viewed as endowing gel-like properties. Collectively, this reasons that efficient, productive and reliable cell signaling takes place primarily through transient, preorganized and cooperative protein–protein interactions spanning the cell rather than stochastic, diffusion-controlled processes.

1. Introduction

A living cell is an organized pattern, structured in space and time (Bolanos-Garcia et al., 2012; Harold, 2005; Nussinov, 2013). Architecture is what ultimately distinguishes a living cell from some haphazard assemblage in solution (McLaughlin et al., 2012). How a cell achieves, preserves, and replicates its spatial organization and how dynamic viable signaling persists within it are fundamental to the understanding of the living state. The cellular architecture is important for the cell's mechanical properties, morphology, motility, metabolism, supramolecular order, chromatin organization and gene expression, trafficking and more. It is also crucial for signaling within and between cells. Signals propagate through interactions; chief among these are between proteins. The cellular organization is hierarchical. Notwithstanding, there is a continuum from small molecular complexes to nanoclusters and membrane domains, to the cytoskeleton (Chen et al., 2014a; Chia et al., 2014); from cell-to-cell interface, to the membrane to the cytoplasm and to the organelles. Such multi-scale organization feeds back to regulate specific proteins, and collectively cell signaling; and at the basic level it does so through dynamic reorganization of multiprotein complexes and assemblies. Dynamic multiprotein complexes are the fundamental unit of cellular organization and signaling. Transient complexes hold the key for the ability of the cell to survive and to respond to its changing environment. Dynamic association implies not merely interactions forming and dissociating; it connotes cooperativity which can specify which interaction takes place at any given time at a given shared binding site. Within this framework, cell signaling can be viewed in terms of dynamic allosteric interactions within and among, spatially organized transient multimolecular complexes.

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The complexes vary over time and space. A key challenge is to understand the interplay across these complexes, link it to the physicochemical basis of the conformational behavior of single molecules, and ultimately relate it to global cellular function. Overall, our thesis is that cell signaling should be thought of as transient, allostery-driven forming and reforming interactions taking place within dynamic, loosely preorganized assemblies, rather than as a sequence of diffusion-controlled molecular collisions (Nussinov, 2013). Growth, differentiation, division, and apoptosis, are temporal; they can be understood only in terms of dynamics within, and among, assemblies and multiprotein complexes. And within this framework, coordination is governed by a conformational biasing mechanism, that is, population shift (Dixit and Verkhivker, 2011; Gunasekaran et al., 2004; Kar et al., 2010; Kumar et al., 2000; Long and Bruschweiler, 2011; Ma et al., 1999, 2002; Rivalta et al., 2012; Shan et al., 2012; Tsai et al., 1999a, 1999b, 2001). Population shift is the origin of allostery; it is the means through which action at the surface of one protein can be expressed by another, far away.

Proteins are often viewed as freely diffusing in the cell. This leads to questions such as how molecules efficiently find their proper location in cell space (Nussinov, 2012). In contrast, here we view cellular signaling as transient pre-organized and interconnected protein assemblies which span the cell, with signaling taking place via dynamic conformational population shifts (Bolanos-Garcia et al., 2012; Nussinov, 2013). Such a multivalent, typically membrane-anchored network, with interactions forming and breaking endows cell signaling with gel-like properties (Fig. 1). We reason that this may well be the efficient, robust, cooperative and controlled signaling system embraced by evolution.

2. A view of cellular organization

Cells are often considered and drawn schematically with proteins encased in a modular organization (Chen et al., 2014b; Resendis-Antonio et al., 2012; Roy et al., 2013; Sohn et al., 2011; Song and Singh, 2013). The underlying premise is that within modules the proteins are likely to be in spatial vicinity, unlike between modules. However to function the module composition needs to change dynamically. Proteins from one module would also need to interact—directly or indirectly—with those in another. Function builds on signaling within and between modules, which can only take place via physical interactions. Here we contend that evolution is unlikely to have cellular communication rely on random diffusion across the large distances in the cell. A random process can place in during basal expression or module (or cluster) re-association of proteins nearby; it is not likely to be productive if the modules are far away. As a cellular signaling mechanism, long distance diffusion can become even more questionable when we consider that cells are organized and structured. They consist of membrane-enveloped organelles and cytoplasm; with functional units either attached to the membrane or partitioned and localized by cytoskeleton proteins (Chen et al., 2014a; Chia et al., 2014). Such a high level of organization optimized by evolution does not appear compatible with micrometer scale diffusion-controlled signaling. Current data point to signaling pathways as complex sets of ordered events; stochastic long distance diffusion would dampen cellular response. The volume excluded by the cytoskeleton increases the crowding and thus the intermolecular association constants which may suggest the feasibility of interaction during a 'random walk' in open space. Such random walks are concentration-dependent, and rely on the ability to move rapidly over long distances (Cebecauer et al., 2010). In contrast, the subnanomolar concentration of growth factors triggering cell stimulation and the concentration of membrane-bound ligands that provoke cellular responses suggest that signaling molecules interact at low concentrations.

Cellular processes need to be regulated. Regulation requires efficiency. Here, we distinguish between multimolecular assemblies and complexes. We define assemblies as large, loose and dynamic multimolecular associations. The assemblies are transient, and freely diffusing molecules may shift to form new assemblies. The molecules are in binding-competent states, poised for direct productive interaction. The assemblies embody smaller multimolecular complexes, which we define as physically interacting molecules. The complexes are similarly transient, dissociating and reassociating, responding to and transmitting cell signals. Clusters can be described as larger and looser bodies such as those of proteins anchored in the membrane rafts and containing lipids. Ras nanoclusters provide one example (Harding and Hancock, 2008; Janosi et al., 2012); T- and B-cell receptors provide another (Molnar et al., 2012). All promote heterogeneous molecular landscapes. Signaling proceeds through a population shift mechanism of the proteins across dynamically pre-organized assemblies, via the direct physical interfaces of the complexes, or mediated by other molecular types, including lipids and water.

While both the population shift and the diffusion-controlled chance collisions mechanisms can co-exist and are not mutually exclusive, signaling is likely to be more productive in pre-organized states (Nussinov, 2013). Accompanied by factors such as protein concentration, cofactors and metabolites, and membrane composition, these may offer an explanation how despite cellular complexity, the cell accomplishes coordination and potent response. The merit of such a view is that it underscores dynamic, transient associations of multiprotein complexes, and provides for a continuum in cell space via inter-connected assemblies and clusters. As we discuss below, these largely take place via scaffolding proteins which bind a large number of partners with different functions; and they do so across a range of scales, including the cytoskeleton (Head et al., 2014). This is amplified by interactions between their partners which are often further supplemented and mediated by the plasma (or organelle) membranes, nucleic acids, ions, water and small molecules such as metabolites and hormones.

3. Multiprotein complexes and the role of allostery

Multiprotein complexes are common in the cell. They fulfill a broad range of functions. They typically contain several enzymes catalyzing successive reactions and in higher organisms are often mediated by scaffolding (or adaptor) proteins as well. The MAPK complex and the E3 system in ubiquitination are two examples. As the case of the KSR1 shows, scaffolding proteins may also function as enzymes (Zhang et al., 2013). Allostery plays a key role in the presence and in the absence of scaffolding proteins (Nussinov et al., 2013a). In the absence of scaffolding proteins, the precise, often short-lived, topographical organization of the enzymes in the complex allows allosteric propagation through the enzyme—enzyme interface which can prime successive enzymatic reactions. A precise organization in the complex is critical; a mere co-localization of the enzymes is non-specific, and cannot achieve such coordination. Nonetheless, such an enzyme-only organization is limited in the range of cellular functional coordination that it can achieve. That however is not the case if scaffolding proteins exist in the complex. Scaffolding proteins can link functions, regulate pathway cross-talk and allow more complex cellular control. Metabolic multiprotein complexes do not appear to contain scaffolding proteins; however, signaling multiprotein complexes usually do. Scaffolding proteins are essential for signal transfer and manipulation. They are active components of multienzyme complexes; much more so than considered by the classical view.