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Review

Actin: From structural plasticity to functional diversity

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ABSTRACT

This article addresses the multiple activities of actin. Starting out with the history of actin's discovery, purification and structure, it emphasizes the close relation between structure and function. In this context, we also point to unconventional actin conformations. Their existence in living cells is not yet well documented, however, they seem to play a special role in the supramolecular patterning that underlies some of the physiological functions of actin. Conceivably, such conformations may contribute to actin's diverse activities in the nucleus that are poorly understood so far.

Actin is a universal protein expressed in all organisms of the present day world. The prototype was originally identified in mammalian muscle. It is quite fascinating to read about the early observations by the physiologists Kuehne (1859) in Heidelberg and Halliburton in London (1887) on contractile "clots" obtained from muscle extracts that were then refined by the biochemists Straub and Szent-Györgyi and in 1942 led to the identification of "actin" as the "substance" capable of activating the ATPase of myosin (reviewed in Schleicher and Jockusch, 2008). In the following years, many actin isoforms and homologues were detected and characterized in cells and tissues from all phyla, most recently in prokaryotes (Van den Ent et al., 2001). According to their closely related structures, manifested in the "actin fold" (Kabsch and Holmes, 1995), actins and actin-related proteins (ARPs) are considered members of the large (and still growing) actin-like ATPase superfamily. The structural homology of actin family members was primarily seen in the fold of their ATP-binding pocket that is also present in families of Hsp70 chaperones and sugar kinases. Consequently, this led to the hypothesis of a common evolution of all these proteins (Bork et al., 1992).

Looking at the history of actin's impact on biological and biomedical research, one notices periods when it was more or less "fashionable" to study the properties and functions of actin. In the beginning, myosin was the more interesting protein for many years. Indeed, at the famous 1971 Cold Spring Harbor Symposium on "The mechanism of muscle contraction" there were only a few contributions about actin, probably the most relevant being the complete sequence of muscle actin by Marshal Elzinga and John Collins (published in Elzinga et al., 1973). However, at this very meeting there was already a session held on "Contractile proteins in non-muscle tissue" with six contributions that heralded the subsequently rapidly evolving area of cytoskeletal research. Right now, we are experiencing a new height in actin research, with a strong focus on the role of actin "nucleators" in the dynamics of actin supramolecular structures.

It goes without saying that the actin world comprises significantly more than actin nucleators. In a eukaryotic cell, the dynamics of actin-based complexes govern vital processes in both, the cytoplasm and the nucleus. A plethora of different proteins that are still increasing in number orchestrate the spatio-temporal control of these phenomena. We yet need to unravel how a rather small, compactly folded protein like actin manages to interact with so many different ligands. A simplified and by far not complete scheme of the different classes of actin binding proteins (ABPs) is presented in Fig. 1. Structural studies have indicated that binding of specific partners to the surface of actin leads to conformational changes in actin itself and/or in polymeric actin assemblies.

Further variability in the actin world is achieved through several actin isoforms that are developmentally regulated or expressed in different tissues, where they might show differential affinity for the same ligand protein. Even when isoforms differ in only very

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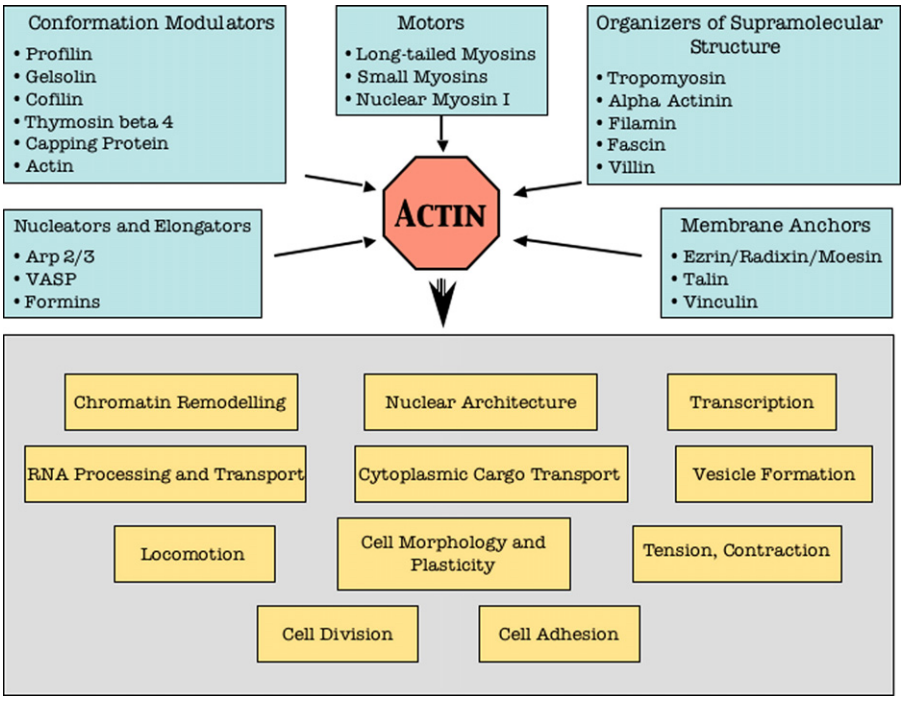

Fig. 1. Actin binding partners that mold actin structures. Actin is indispensable for many different processes in the nucleus and in the cytoplasm of eukaryotic cells (depicted in yellow). To perform this multitude of tasks it has to interact with a wide variety of actin-binding proteins (ABPs) – including itself – that regulate its conformation, polymerization and supramolecular conformation in many ways. So far, at least 150 different ABPs are known of which only a selection is listed (blue boxes).

few residues, they cannot fully substitute each other in tissue-specific functions. In addition, actin may be posttranslationally modified, for example by methylation, Ser/Thr or Tyr phosphorylation, acetylation, acylation or ubiquitination. ADP-ribosylation of specific residues of the host actin is another strategy followed by several pathogenic bacteria to improve their survival (Aktories et al., 2011; Lang et al., 2010).

Actin shares its structural plasticity with another important, ubiquitously expressed protein, tubulin (see for example Kirschner, 1978). Under physiological conditions, tubulin and actin show a preference for one particular supramolecular structure that is the product of a polymerization process. For actin, this is the "conventional" double helical filament called F-actin. Based on its structure, its dynamic behavior and its ability to participate in a great variability of supramolecular assemblies, F-actin is engaged in the majority of actin functions. However, there is now growing evidence that there are other actin conformations that may also be involved in important cellular processes. One avenue to understanding actin's action in different cellular functions started with elucidating its molecular anatomy.

Struggling with the structure

In the second half of the last century, cytoskeletal proteins could already be isolated in large quantities and reasonable purity, allowing many laboratories to attempt crystallization for 3D-structure determination. Unfortunately, actin turned out to elude these attempts by rapidly polymerizing into filaments at the salt condition needed for crystal growth. The breakthrough came from a fortuitous observation: it was Uno Lindberg who crystallized a protein complex from bovine spleen that was able to inhibit deoxyribonuclease I (DNase I; Lindberg, 1967), not knowing at that time that the proteinaceous inhibitor of DNase I would later turn out to be actin (Lazarides and Lindberg, 1974). The biological significance of the interaction of DNase I, a secreted enzyme, and the intracellular structural protein actin is still a mystery, although the extremely high affinity suggests some functional importance. In addition to actin, the inhibitory complex isolated from spleen contained another protein termed profilin. Crystallization of the 1:1 complex of cytoplasmic actin and profilin was reported in 1976 (Carlsson et al., 1976). Both studies demonstrated that when prevented from polymerization by a protein ligand, actin could be forced to form crystals. Subsequently, crystallization of actin complexed with bovine DNase I was reported (Mannherz et al., 1977). However, it took another 14 years to arrive at a low resolution structure of the actin:DNase I complex that clearly defined the actin and DNase I moieties (Suck et al., 1981) and 10 more years until the high resolution (2.8 Å) structure of the actin:DNase I complex was completed (Kabsch et al., 1990). Structure determinations of chemically modified actins, different isoforms, ARPs or bacterial homologues, mutated variants, or in complex with various ABPs followed in rapid succession (see also Dominguez and Holmes, 2011). Meanwhile the atomic structure of actin has been solved about 80 times. All structures determined so far basically confirmed the initially proposed structure of skeletal (alpha-) actin in complex with DNase I (Kabsch et al., 1990).

The molecular anatomy of G- and F-actin

It is undisputed that the diversity of actin's physiological functions is based on its structure and thus we recapitulate some of the basic facts. The actin molecule (G-actin) is composed of a single polypeptide chain of 375 residues that is folded into two almost equally sized domains separated by a deep cleft that harbors a binding pocket for small molecules like nucleotides or phalloidin (see below). Each main domain can be further divided into two subdomains (SD), resulting in SD1–SD4. Fig. 2A shows the standard ("butterfly") front view of actin. All SD contain a central beta-sheet surrounded by a varying number of alpha helices. G-actin is a flat molecule as shown by the side-view in Fig. 2B, with dimensions of about $55 \times 55 \times 35$ Å. The bound nucleotide is located at the bottom of the deep cleft (Fig. 2A). Here the peptide chain crosses twice