FEBS Letters 587 (2013) 1053–1061

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Influence of crowded cellular environments on protein folding, binding, and oligomerization: Biological consequences and potentials of atomistic modeling

Huan-Xiang Zhou

Department of Physics and Institute of Molecular Biophysics, Florida State University, Tallahassee, FL 32306, USA

ARTICLE INFO

Article history:
Received 10 January 2013
Accepted 28 January 2013
Available online 5 February 2013

Edited by Wilhelm Just

Keywords:
Macromolecular crowding
Protein folding
Protein binding
Protein aggregation
Postprocessing

ABSTRACT

Recent experiments inside cells and in cytomimetic conditions have demonstrated that the crowded environments found therein can significantly reshape the energy landscapes of individual protein molecules and their oligomers. The resulting shifts in populations of conformational and oligomeric states have numerous biological consequences, e.g., concerning the efficiency of replication and transcription, the development of aggregation-related diseases, and the efficacy of small-molecule drugs. Some of the effects of crowding can be anticipated from hard-particle theoretical models, but the *in vitro* and *in vivo* measurements indicate that these effects are often subtle and complex. These observations, coupled with recent computational studies at the atomistic level, suggest that the latter detailed modeling may be required to yield a quantitative understanding on the influence of crowded cellular environments.
© 2013 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.

1. Motivation and scope

It is now widely recognized that the crowded conditions found in cellular environments can significantly impact the equilibria and kinetics of biochemical processes such as protein folding, binding, and oligomerization. Pioneering work by Minton [1], Kornberg [2], Ellis [3], and others as well as many recent studies have contributed to this recognition. As more and more researchers pay attention to and start to study the effects of crowded conditions, questions of general interest include: What has been established by studies of crowding? How best can we advance the quantitative understanding on the influences of the crowded cellular environments? This review presents a personal view on these and related questions.

A few studies have presented dramatic effects of macromolecular crowding. In Arthur Kornberg's lab, many failed attempts finally led to success in replicating the *oriC* plasmid in a cell-free condition, upon including a high concentration of polyethylene glycol (PEG) in the incubation mixture [4]. As Kornberg [2] lucidly explained later, "the PEG gel occupies most of the aqueous volume and excludes a small volume into which large molecules are crowded. This concentration is essential when several proteins are needed in the consecutive steps of a pathway." Hence Kornberg made "Thou Shalt Correct for Extract Dilution with Molecular Crowding" one of his ten commandments as he reflected on his studies of DNA replication.

More recently several labs observed that crowding agents such as PEG, Ficoll, and dextran drastically increased the aggregation rates of α-synuclein [5,6] and apolipoprotein C-II [7], and enabled the efficient assembly of the HIV-1 capsid protein [8] and the alignment of FtzZ filaments into ribbons [9]. Red blood cells contain high concentrations (~320 g/l) of hemoglobin, and such a level of crowding is an essential condition for sickle hemoglobin (HbS) polymerization and sickle cell anemia [10]. A 20% reduction in the HbS concentration could reduce the rate of homogeneous nucleation of HbS into polymers by as much as 10^{10}-fold. Fetal hemoglobin (HbF) is unable to polymerize and replacement of HbS by HbF presents a potential therapy for sickle cell anemia. Ironically, as the HbF replacement essentially preserves the crowding effects, a 20% HbS-to-HbF replacement results in only a 10^3-fold reduction in the rate of homogeneous nucleation, which would render HbF replacement an ineffective therapy.

In contrast to the foregoing studies, the effects of crowding found in many other studies are modest. For example, a number of papers [11–16] reported small increases, of the order of 1–2 k_BT (k_B: Boltzmann constant; T: absolute temperature), in protein

Abbreviations: BPTI, bovine pancreatic trypsin inhibitor; BSA, bovine serum albumin; CI2, chymotrypsin inhibitor 2; HbF, fetal hemoglobin; HbS, sickle hemoglobin; HSQC, ^{1}H–^{15}N heteronuclear single quantum coherence; IDP, intrinsically disordered protein; PEG, polyethylene glycol; PVP, poly(vinylpyrrolidone)

E-mail address: hzhou4@fsu.edu

0014-5793/$36.00 © 2013 Federation of European Biochemical Societies. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.febslet.2013.01.064

folding stability by crowding agents. Similar results were found for the effects of crowding agents on the binding stability of protein–protein heterodimers [17,18]. Two issues then arise: Can the dramatic effects of crowding observed in some studies be reconciled with the subtle effects found in other studies? Do these subtle effects of crowding nevertheless have biological significance?

Statistical thermodynamics provides a conceptual framework for addressing these issues and for a fundamental understanding of how crowding affects various biochemical processes. In principle, the equilibrium properties of these processes are determined by the energies of interactions within and between the "reactant" molecules and between the reactant molecules and bystander molecules such as crowders; kinetic properties require in addition information on the dynamics of the reactant molecules in the solvent environment [19]. In practice, until recently, calculations of the effects of crowding on thermodynamic and kinetic properties were only possible using simple models based on a hard-particle representation of reactant and crowder molecules, with excluded-volume interactions playing a dominant role [20,21]. Molecular simulations have now opened a powerful way to model the effects of crowding, and promise to enable quantitative predictions on the influences of the crowded cellular environments.

The following sections present a critical assessment of some recent studies of biochemical processes in cells and in crowded solutions, with an eye toward answering the two questions posed in the opening paragraph. I mostly limit to studies that appeared in the last four years. Earlier studies are covered in several reviews [22–26], and some are already mentioned in the preceding paragraphs. In addition, the focus is on equilibrium properties; effects of crowding on kinetic properties are assessed elsewhere [19,21,23,27–30]. Experimental studies, divided into three sections, are followed by computational studies in a single section.

2. Protein folding

Upon synthesis, most, not all, proteins fold into defined 3-dimensional structures before gaining biological functions (Fig. 1). Some others exist as unstructured in one functional state and structured in another (e.g., when bound to a biological target). Extending other studies [11–14,16], the Pielak lab has assessed how crowded cytomimetic conditions affect the folding stability of proteins [15,31–34]. These recent studies are notable both for the experimental technique used and for their findings, presenting additional subtleties and complexities of the effects of crowding. The technique is NMR-detected amide proton exchange, which probes residue-level local stability, i.e., the stability of individual residues to withstand opening up for hydrogen/deuterium exchange [35]. Opening of the residues with the highest local stability involves global unfolding; hence the highest local stability corresponds to the global folding stability.

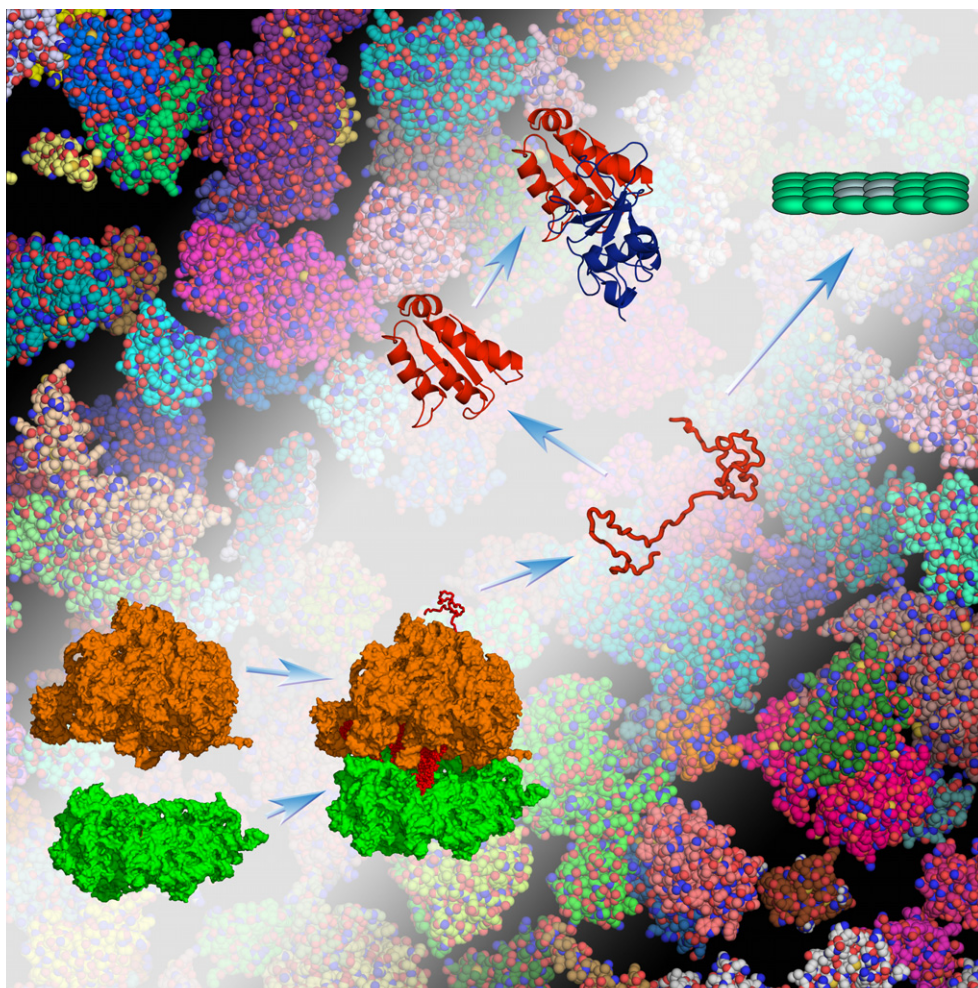

Fig. 1. Inside cells biochemical processes occur in crowded environments. The depicted processes include the binding of the large and small subunits of the ribosome, the folding of a nascent protein, its binding to another protein, and aggregation. The crowded conditions can significantly change the relative stability among the various species.

Download English Version:

https://daneshyari.com/en/article/10871028

Download Persian Version:

https://daneshyari.com/article/10871028

Daneshyari.com