

Interaction, assembly and processing At the chemistry–biology interface

Editorial overview

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Abbreviations

bZIP basic zip leucine zipper
TBP TATA box binding protein
TF transcription factor

Few events that transpire in biology are unimolecular processes. Nowhere is this observation more apparent than in the processes that generate a functional protein from a gene. The gene is first transcribed and edited into mature mRNA by multicomponent protein and ribonucleoprotein assemblies. The edited mRNA is then translated into protein by the ribosome, the quintessential multicomponent enzyme. Finally, the newly translated protein is processed into a mature, functional form by a variety of enzymes and shuttled to the correct compartment of the cell. Even degradation of unneeded proteins to replenish amino acid reserves is performed by a multisubunit proteasome. This section of *Current Opinion in Chemical Biology* highlights recent advances in understanding the chemical biology of covalent and noncovalent interactions that define important assembly and processing events during the production of functional proteins.

The centrality of assembly in cellular processes is well illustrated in the case of the transcription apparatus. Much of the control of gene regulation occurs in the early stages of preinitiation complex formation. Indeed, it is generally believed that the rate of association of the TATA box binding protein (TBP) with the TATA box can, in some cases, limit the rate at which transcription proceeds. Thus, understanding the factors that control this rate may be of practical importance for the design of transcription inhibitors. Cox *et al.* (pp 11–17) highlight the application of physical organic and biochemical approaches to characterize the kinetics and specificity of TBP–TATA box assembly. These studies emphasize that the extent to which TBP (or TFIID (transcription factor IID)), as well as the extent of DNA bending in the TBP–TATA box complex (and eventually the rate of transcription itself)

could be regulated by interactions with other factors, many of which remain to be identified.

Transcription factors are proteins that bind to DNA upstream of the preinitiation complex, forming assemblies that may also include other proteins known as accessory factors. The review by Baranger (pp 18–23) on interactions between accessory factors and basic region leucine zipper (bZIP) proteins summarizes progress made in deciphering the rules that govern assembly and gene regulation by these factors. The small size of the bZIP element, coupled with its structural simplicity (a dimer of extended helices each of which comprises about 60 amino acids), makes detailed analysis possible and allows bZIP proteins to serve as models for considering more complex motifs.

Once the transcriptional apparatus has successfully produced messenger RNA, the translational apparatus can begin converting this message into protein. Several lines of evidence support a critical role for ribosomal RNA in the peptidyl transferase reaction that forms new peptide bonds during translation, although it is still not clear whether the essential catalytic residues reside on a ribosomal protein, a ribosomal RNA, or on both macromolecules. Regardless of the role of RNA in the assembly of new proteins, the role of RNA in the processing of newly transcribed RNA molecules is well appreciated. These processing pathways can follow a variety of interesting mechanisms, and it is hoped that an increased understanding of these mechanisms will assist in the creation of *trans*-acting ribozymes that have potential as useful biological reagents or possibly even as drugs. Walter and Burke (pp 24–30) review the hairpin ribozyme, which consists of two independently folding domains that interact through tertiary contacts facilitated by metal ions.

Many macromolecules are not synthesized in a fully functional form but must first be processed into shorter or more highly decorated forms in order to attain full biological activity. A classic example is the post-translational proteolytic processing of a prohormone, such as proinsulin, to generate the active hormone. Steiner (pp 31–39) reviews recent developments in our understanding of the structure, mechanism and function of the proprotein convertase enzymes that catalyze these cleavage reactions. Many peptide hormones also undergo an oxidative processing event at their carboxyl termini, the mechanism of which has been subject to considerable research. The first step in this two step reaction can now be analyzed in atomic detail, thanks to the recently reported

high resolution structure of a peptidyl α -hydroxylating monooxygenase domain. Understanding the mechanism of oxidative protein processing may also provide clues to the chemical basis of oxidative protein damage, as well as aid in the design of drugs for diseases ranging from rheumatoid arthritis to cancer.

Vital events take place at membrane surfaces that could not, or would not, occur in the general cellular milieu. Targeting of specific molecules to membranes is believed to be facilitated by a third type of post-translational processing event that involves the covalent attachment of membrane-anchor moieties to newly synthesized proteins. Gelb and co-workers (pp 40–48) discuss our understanding of the structure, function and inhibition of protein prenyltransferase enzymes that decorate newly synthesized proteins with farnesyl and geranylgeranyl groups. The authors conclude that considerable work remains to elucidate the complete range of biological functions conferred by protein prenylation. Nevertheless, the important role of farnesylated Ras in neoplastic transformation has stimulated the development of a wide variety of farnesyltransferase inhibitors. Some of these molecules are being evaluated in preclinical trials as anti-cancer drugs.

A final example of post-translational processing, the fundamentals of which are finally yielding to detailed analysis is the covalent attachment of carbohydrates during the construction of glycoproteins. The review by Yarema and Bertozzi (pp 49–61) focuses on chemical approaches to understanding the molecular details of carbohydrate–protein recognition events and emerging approaches to target carbohydrate interactions as a ther-

apeutic strategy. Yarema and Bertozzi also discuss the exciting finding that chemically-defined carbohydrates can be presented on the surfaces of mammalian cells. This technique should allow the parallel construction of cell libraries in which the members differ only in terms of the appended carbohydrate component. Such libraries should find use in screening oligosaccharides for receptor-binding activity and for revealing fundamental kinetic and thermodynamic details of carbohydrate–ligand interactions.

Finally, it is commonly thought that the task of inhibiting the assembly of a protein–protein interface will be considerably more difficult than that of inhibiting an enzyme active site. The reasoning is that active sites are often located within clefts in the protein surface, in which small molecules can use much of their three-dimensional surface to make a small number of favourable contacts. In contrast, protein–protein interfaces are often large and flat. It must be pointed out, however, that regardless of the molecular terrain the rules of Gibbs apply, and any molecule with sufficient affinity for a protein–protein interface will inhibit assembly, regardless of the shape of the interface. The relevant considerations for what constitutes ‘sufficient affinity’ are the intrinsic affinity for the target protein and the concentration of each component. In their review, Zutshi *et al.* (pp 62–67) examine the state of inhibitors that function by interfering with protein assembly. Some designed peptide inhibitors of HIV protease have inhibition constants in the nanomolar concentration range. Evidence that small molecule assembly inhibitors hold considerable promise for the future is provided by recent success in generating orally available lead compounds from peptide inhibitors.