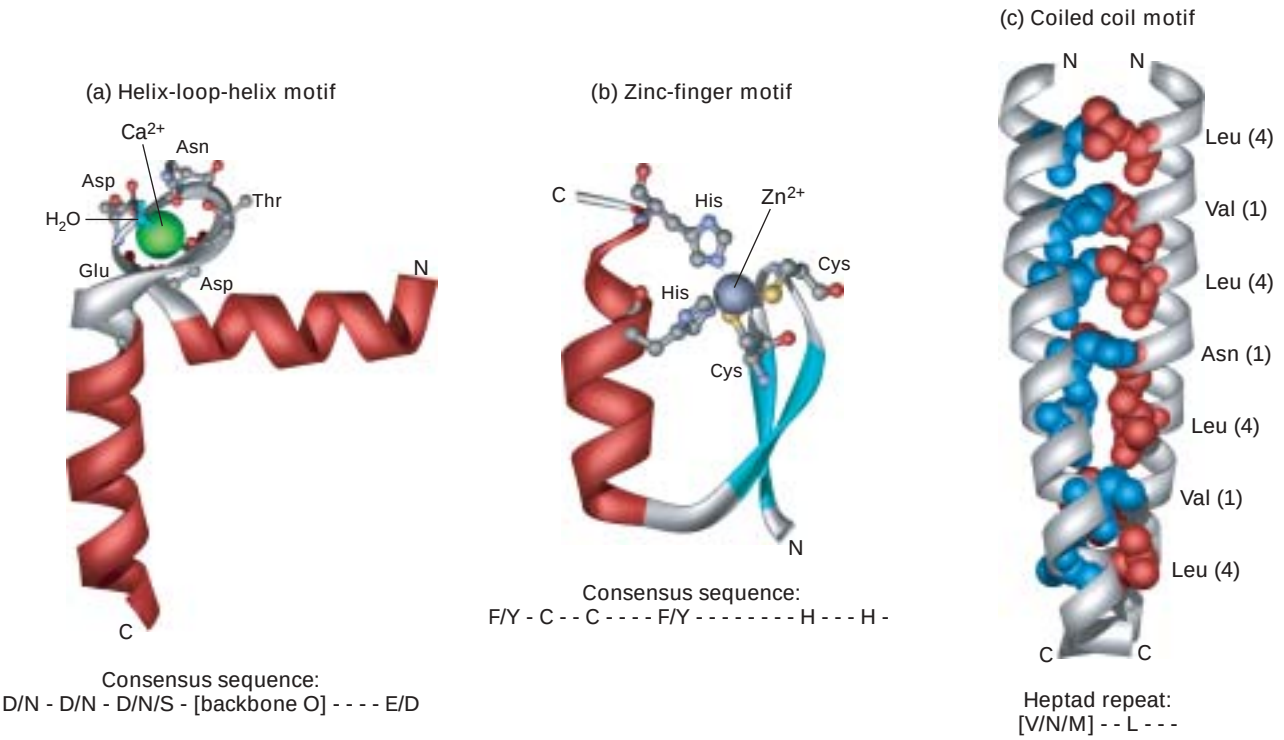

▲ FIGURE 3-6 **Motifs of protein secondary structure.** (a) Two helices connected by a short loop in a specific conformation constitute a helix-loop-helix motif. This motif exists in many calcium-binding and DNA-binding regulatory proteins. In calcium-binding proteins such as calmodulin, oxygen atoms from five loop residues and one water molecule form ionic bonds with a Ca^{2+} ion. (b) The zinc-finger motif is present in many DNA-binding proteins that help regulate transcription. A Zn^{2+} ion is held between a pair of β strands (blue) and a single α helix (red) by a pair of cysteine residues and a pair of histidine residues. The two invariant cysteine residues are usually at positions 3 and 6 and the two invariant histidine residues are at positions 20 and 24 in this 25-residue motif. (c) The parallel two-stranded coiled-coil motif found in the transcription factor Gcn4 is characterized by two α helices wound around one another. Helix packing is stabilized by interactions between hydrophobic side chains (red and blue) present at regular intervals along the surfaces of the intertwined helices. Each α helix exhibits a characteristic heptad repeat sequence with a hydrophobic residue at positions 1 and 4. [See A. Lewit-Bentley and S. Rety, 2000, EF-hand calcium-binding proteins, *Curr. Opin. Struct. Biol.* **10**:637–643; S. A. Wolfe, L. Nekludova, and C. O. Pabo, 2000, DNA recognition by Cys2His2 zinc finger proteins, *Ann. Rev. Biophys. Biomol. Struct.* **29**:183–212.]

combinations of secondary structures have been conserved in evolution. To date, hundreds of motifs have been cataloged and proteins are now classified according to their motifs.

Structural and Functional Domains Are Modules of Tertiary Structure

The tertiary structure of proteins larger than 15,000 MW is typically subdivided into distinct regions called **domains.** Structurally, a domain is a compactly folded region of polypeptide. For large proteins, domains can be recognized in structures determined by x-ray crystallography or in images captured by electron microscopy. Although these discrete regions are well distinguished or physically separated from one another, they are connected by intervening segments of the polypeptide chain. Each of the subunits in hemagglutinin, for example, contains a globular domain and a fibrous domain (Figure 3-7a).

A structural domain consists of 100–150 residues in various combinations of motifs. Often a domain is characterized by some interesting structural feature: an unusual abundance of a particular amino acid (e.g., a proline-rich domain, an acidic domain), sequences common to (conserved in) many proteins (e.g., SH3, or Src homology region 3), or a particular secondary-structure motif (e.g., zinc-finger motif in the kringle domain).

Domains are sometimes defined in functional terms on the basis of observations that an activity of a protein is localized to a small region along its length. For instance, a particular region or regions of a protein may be responsible for its catalytic activity (e.g., a kinase domain) or binding ability (e.g., a DNA-binding domain, a membrane-binding domain). Functional domains are often identified experimentally by whittling down a protein to its smallest active fragment with the aid of proteases, enzymes that cleave the polypeptide backbone. Alternatively, the DNA encoding a protein can be