CHAPTER

31

Antibody Structure and Recognition of Antigen

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Antibodies may be regarded as products of a protein engineering system for the generation of a virtually unlimited repertoire of complementary molecular surfaces. This extreme structural heterogeneity is required for recognition of the infinite array of antigenic determinants presented in nature. Here we discuss broadly the structure of antibodies and their specific recognition of antigens, the binding energetics of antibody–antigen interactions, the structural basis of the antibody maturation process, and limitations to antibody affinity and specificity for antigens.

A STRUCTURAL FRAMEWORK FOR MOLECULAR RECOGNITION

Antibody molecules (Figure 31.1) are composed of two identical polypeptide chains of approximately 500 amino acids (the heavy or H chains) covalently linked through disulfide bridges to two identical polypeptide chains of roughly 250 residues (the light or L chains). Based on amino acid sequence comparisons, the H and L chains may be divided into N-terminal variable (V) and C-terminal constant (C) portions. Each H chain contains four or five domains (V_H, C_H1, C_H2, $C_H3 \pm C_H4$ depending on the antibody isotype) of two anti-parallel β-sheets, whereas each L chain consists of two such domains (V_L, C_L). The V_L and C_L domains are disulfide-linked with the V_H and C_H1 domains, respectively, to form the Fab region of the antibody, which is linked through a hinge region to the Fc domain, formed by noncovalent association of the C_H2–4 domains from both chains. All of the β-sheet domains are structurally very similar and belong to the "immunoglobulin fold" superfamily (Amzel and Poljak, 1979), a structure that is not unique to antibodies but is utilized by numerous immunoreceptors. The V_H and V_L domains each contain three segments, or loops, which connect the β-strands and are highly variable in length and sequence among different antibodies (Wu and Kabat, 1970). These so-called complementarity-determining regions (CDRs) lie in close spatial proximity on the surface of the V domains and determine the conformation of the combining site. In this way, the CDRs confer specific binding activity to the antibody molecule. The central paradigm of antibody–antigen recognition is that the three-dimensional structure formed by the six CDRs recognizes and binds a complementary surface (epitope) on the antigen.

Although CDR loops are hypervariable and confer binding specificity to the antibody, it is not necessary that all six CDR loops interact with a given antigen. Antibodies to smaller antigens, such as haptens and peptides, commonly do not utilize all six CDRs (Chitarra et al., 1993; Wilson and Stanfield, 1993), whereas anti-protein antibodies nearly always do. Camelid antibodies that have no light chains (Hamers-Casterman et al., 1993) but can, nonetheless, bind protein antigens with nanomolar affinities using as few as two CDR loops (Decanniere et al., 1999) are a clear exception to this generality. Framework regions are commonly invoked in antigen recognition to varying degrees, and can comprise up to 15% of the buried surface area of an antibody–antigen complex (Wilson and Stanfield, 1994). The V_HCDRs, and V_HCDR3 in particular, generally make more extensive contacts than V_LCDRs, and the geometrical center of the interface tends to lie near V_HCDR3. There exists a strong correlation between residues that do not form contacts with antigen and those residues that are important in defining the canonical backbone structures of the CDR loops (Chothia et al., 1989). These residues tend to pack internally and are therefore less exposed on the antibody combining site surface.