Sondermann et al., 2000). Progressively higher resolution has allowed the generation of more refined models. An α-carbon ribbon structure for a human IgG1 molecule is shown in Figure 4.1.

The observed internal mobility of the lower hinge and hinge proximal regions of the C_H2 domains allows for an equilibrium of high-order conformers to be formed that may differentially bind unique ligands (e.g., the three homologous Fcγ receptor types). Previous proposals that different ligands may bind through "overlapping nonidentical sites" may suggest too rigid a structure and may be modified to propose that each FcγR binds to a unique IgG-Fc conformer present within an equilibrium of transient protein structures. However, amino acid residue side chains and/or main chain atoms may be involved in common (Anumula, 2012; Jefferis, 2012; Jefferis et al., 1998; Ozbabacan et al., 2011). The binding sites for sFcγRIIa, sFcγRIIIa, and sFcγRIIIb are asymmetric, with both heavy chains being engaged such that monomeric IgG is univalent for each Fcγ receptor and the C1 component of complement. This obviates continuous activation of inflammatory cascades by circulating endogenous monomeric IgG *in vivo*; IgG antigen/antibody immune complexes are multivalent and able to cross-link and activate cellular receptors. Residues of the lower hinge region that are disordered in the Fc crystals are ordered in the Fc-sFcγR complexes and are directly involved in binding the receptor (Frank et al., 2014; Radaev

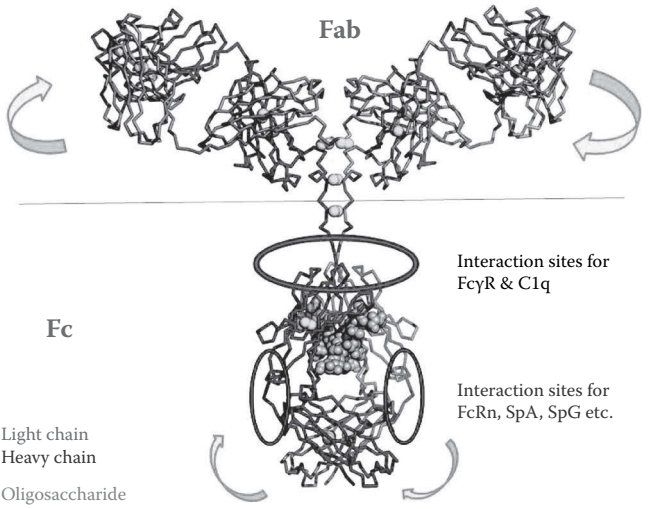

FIGURE 4.1 **(See color insert.)** An α-carbon cartoon of a human IgG1 molecule indicating binding sites for IgG1-Fc ligand binding sites; arrows indicate independent mobility of Fab & Fc around the hinge region. (1) The C_H3 domains are well defined due to noncovalent pairing, in the $(C_H3)2$ module; (2) There is a significant area of noncovalent contact between the C_H2 and C_H3 domains that stabilizes the C_H2/C_H3 interdomain structure; (3) The C_H2 domains do not pair, and the hydrophobic surface of each C_H2 domain is "overlaid" by the carbohydrate; (4) the structure in the hinge proximal region of the C_H2 domain is, relatively, disordered; (5) The intrinsic stability of the immunoglobulin fold is reflected in higher structural resolution for the β-sheets regions than for β-bends. (Courtesy of Peter Artymiuk, University of Sheffield, using PyMol: http://pymol.sourceforge.net.)