Minor glycoforms present in polyclonal IgG-Fc may be biologically significant since each could be the predominant glycoform of an individual antibody secreted from a single plasma cell; analysis of monoclonal human IgG, isolated from the sera of a patient with plasma cell cancer (multiple myeloma), has shown that the IgG-Fc glycoform profile of the paraprotein is essentially unique for each protein analyzed (Farooq et al., 1997; Jefferis et al., 1990; Kibe et al., 1996). Subtle differences in oligosaccharide processing is observed, with a preference for addition of galactose to the α(1–6) arm of IgG1-Fc and the α(1–3) arm of IgG2-Fc; the arm preference for IgG3 correlates with an allotypic difference, the presence of tyrosine or phenylalanine at residue 296 (Y296F), immediately adjacent to asparagine 297 (Alavi et al., 2000; Ercan et al., 2010; Jefferis, 2012). These data suggest a critical balance between the conformation of the IgG-Fc and the steric requirements of glycosyltranferases that may be sensitive to niche environments within the Golgi apparatus.

The glycoform profile of serum polyclonal IgG can vary significantly in both health and disease states, particularly in autoimmune and inflammatory diseases (Alavi et al., 2000; Ercan et al., 2010; Farooq et al., 1997; Hayes et al., 2014; Jefferis, 2009a, 2012; Jefferis et al., 1990; Kibe et al., 1996). Methodologies that allow the glycoform profile of antigen-specific serum IgG antibodies to be determined demonstrate significant glycoform profile differences between IgG autoantibodies and the bulk IgG (Holland et al., 2006; Rombouts et al., 2015; Wuhrer et al., 2015). The oligosaccharide profiles of recombinant IgG proteins produced in mammalian cells differ between cell types, the culture method, and precise medium conditions employed. For mAbs the [G0F/G0F] glycoform predominates (see below). Under conditions of stress (e.g., nutrient depletion, acid pH, etc.), deviant glycosylation may be observed (e.g., the presence of high mannose forms and/or incomplete site occupancy) (Bondt et al., 2013).

4.14 IgG-Fc PROTEIN/OLIGOSACCHARIDE INTERACTIONS

The Deisenhofer IgG-Fc structure suggested the potential for 72 protein/oligosaccharide interactions, including six C_H2 protein/oligosaccharide hydrogen bonds and six hydrogen bonds within each oligosaccharide moiety (Corper et al., 1997; Deisenhofer, 1981; Frank et al., 2014; Jefferis, 2012; Padlan, 1990; Radaev et al., 2001; Ramsland et al., 2011; Sauer-Eriksson et al., 1995; Sondermann et al., 2000). These interactions include the sugar residues of the α(1–6) arm, while residues of the α(1–3)-Man-GlcNAc arms are orientated toward the internal space between the C_H2 domains; weak lateral interactions between sugar residues present on opposed heavy chains have been suggested for some structures (Corper et al., 1997; Deisenhofer, 1981; Frank et al., 2014; Jefferis, 2012; Padlan, 1990; Radaev et al., 2001; Ramsland et al., 2011; Sauer-Eriksson et al., 1995; Sondermann et al., 2000).

Structural and functional studies of normal, truncated, and aglycosylated glycoforms of IgG1-Fc, generated *in vitro*, have employed X-ray crystallography (Corper et al., 1997; Deisenhofer, 1981; Frank et al., 2014; Padlan, 1990; Radaev et al., 2001; Ramsland et al., 2011; Sauer-Eriksson et al., 1995; Sondermann et al., 2000), differential scanning microcalorimetry (DSC), and Fcγ receptor binding (isothermal