

(Figure 1.2(c)). Although these chains are buried within the mAb Fc structure they can be removed using PNGase F (Weitzhandler, Hardy, Co, & Avdalovic, 1994), and this is likely due to the flexibility and mobility between the Fc heavy chains. The carbohydrates play a huge role in governing the so-called “cell effector function” (Jefferis, Lund, & Pound, 1998; Mattu et al., 1998; Mimura et al., 2001). In particular, if the oligosaccharides are removed from the IgGs they no longer can bind to C1q, the first component of the complement cascade, as well as cellular receptors such as FcγRI, II, and III, which are used to activate immune cells (Wang et al., 2007). In addition to modulating immune function the carbohydrates impact conformation, stability, and immunogenicity of the IgGs (Tao & Morrison, 1989; Wang et al., 2007; Wen, Jiang, & Nahri, 2008). Although aglycosylated mouse/human chimera IgGs are still able to bind to target antigens as well as protein A, and appear to be properly assembled, they are generally more sensitive to protease than their corresponding IgG1 with oligosaccharides (Tao & Morrison, 1989).

Although mAbs are monoclonal, having been derived from one cell line, the manufactured DS can be very heterogeneous due to differences in glycosylation, errors in transcription or translation during cellular protein synthesis resulting in misincorporation of amino acid residues, and posttranslational processing (Guo et al., 2010; Liu, Gaza-Bulseco, Faldu, Chumsae, & Sun, 2008). The glycosylation in mAbs is a result of an enzymatic reaction, which occurs in cells, and differences in glycosylation occur during protein synthesis. Differences in glycosylation pattern are also dependent on the species used for expression of the mAb (Raju, Briggs, Borge, & Jones 2000). The most common posttranslational processes leading to heterogeneity include incomplete disulfide formation as well as C-terminal processing whereby lysine residues are removed (Liu et al., 2008).

Overall, IgG mAbs are complex molecular machines capable of selectively binding to targets. The hinge region, especially in IgG1 mAbs, confers substantial flexibility to the molecule and can impact stability and function of these therapeutic agents. The next chapter will discuss stability of this important class of biotherapeutics.

## References

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