Stability of monoclonal antibodies (mAbs)

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Degradation routes in monoclonal antibodies

Many of the degradation reactions and routes that govern monoclonal antibody (mAb) stability are essentially the same as found in proteins. Some important differences between the general class of proteins and mAbs are due to the greater flexibility of mAbs related to the hinge region between Fab and Fc domains. An overall schematic of protein degradation routes shows that protein can degrade via alterations in physical as well as chemical attributes (Figure 3.1). Although chemical and physical degradation routes are often depicted as separate events they, in fact, can correlate in their impact on stability. As an example, chemical degradation routes can alter conformation, which in turn may result in formation of protein aggregates. Likewise a local conformational change may impact environments around chemically susceptible amino acid residues resulting in enhancement of degradation kinetics. There are many reviews on protein stability (Cleland, Powell, & Shire, 1993; Jaenicke, 2000; Manning, Chou, Murphy, Payne, & Katayama, 2010; Manning, Patel, & Borchardt, 1989; Oliyai, Schoneich, Wilson, & Borchart, 1992; Wang & Hanson, 1988) and a mini review on mAb stability (Wang, Singh, Zeng, King, & Nema, 2007). Here we summarize the main degradation routes for proteins, and specifically mAbs.

Chemical degradation

Chemical degradation involves alterations in amino acid residues, which are covalent in nature. The most common chemical degradation routes are oxidation, deamidation, Asp isomerization, and cross-linking. The chemical changes that occur may or may not impact the activity of the protein since it depends on the site of the chemical change. The alteration of a residue in an active site or binding pocket for ligand may result in a local change such as a conformational or charge change, which impacts the function of the specific site. Examples of such specific changes that result in loss of binding include an Asp isomerization in Xolair®, a mAb used for treatment of asthma (Cacia, Keck, Presta, & Frenz, 1996), and an Asn deamidation in Pulmozyme®, a protein used in the treatment of cystic fibrosis (Shire, 1996). A chemical change can also result in a change in function or activity due to aggregation promoted by an amino acid residue alteration, such as in loss of solubility and hence activity of human relaxin due to oxidation (Li, Nguyen, Schoneich, & Borchardt, 1995; Khossravi, Shire, & Borchardt, 2000).

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