MS04 Structure in Cancer Biology

MS4-01
Conformational regulation in anti-CD40 antibodies
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Abstract
Antibodies are an increasingly important therapeutic modality comprising ~eighty percent of therapeutic biologics. Despite this, further improvements in therapeutic antibody design are required. Although the majority of the 100+ antibodies approved for use in the clinic are of the hIgG1 isotype, other isotypes are now being increasingly investigated. For example, the hIgG2 isotype is unique in its ability to exhibit a range of different disulfide orientations in its hinge region which may afford additional therapeutic functionality. While this is a natural phenomenon, occurring in the blood through a red-ox process, it can also be exploited in therapeutic antibodies to enhance signalling (agonism) of certain important immune receptor targets, such as CD40. However, the underpinning mechanism is unknown.

Therefore, here, we studied the hinge of hIgG2 in the context of the clinically relevant anti-CD40 monoclonal antibody chiLob7/4. Cysteines in the hinge region were exchanged to serine in a number of different variants with subsequent biological activity and hinge disulfide structure evaluated using an anomalous scattering approach. In these anti-CD40 Lob7/4 hIgG2 antibodies, which all bind to the same epitope and retain high affinity binding, activity correlated with formation of a specific disulfide crossover structure. SAXS analysis showed that the crossover restricts conformational freedom of the antibody. A full-atomistic simulation and evaluation of the conformational pool against the SAXS data using ensemble methods showed that fewer conformations exist in solution in antibodies that are agonistic. This study highlights that specific modifications of monoclonal antibody hinge regions to introduce covalent disulfide links can modulate receptor signalling in an epitope-independent manner, which may be applicable in future therapeutics.

References
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