

Probing Antigen Structure and Antigen-Antibody Interactions by Synchrotron Radiation and Mass Spectrometry

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The human immune system provides protection against both intracellular and extracellular pathogens, malignancy and autoimmune diseases. The vast majority of pathogens or invasive agents associated with immune disorders and disease are attributed to protein molecules. The role of the humoral or B-cell response is to destroy extracellular pathogens and prevent the spread of infection from cell to cell. A key feature of this response is the molecular complementarity of antigen and antibody. Mature B cells secrete antibodies that bind to the native antigen in a highly conformation-dependent process. In order to fully understand these aspects of the immune response and exploit this knowledge in, for example, the development of vaccines, it is necessary to characterize an antigen's tertiary structure and the influence this has on its interaction with antibody. We are developing a radically new approach for characterizing protein antigens at the picomole and sub-picomole level using synchrotron radiation and mass spectrometry. Time-resolved synchrotron radiolysis on a millisecond time scale has previously been shown to be a powerful method for studying RNA conformation and folding with single base resolution. In the case of proteins, amino acid side chains are modified by X-ray radiolysis and these modifications are influenced in part by the accessibility of the sites to the bulk solvent. Mass spectrometric techniques are used to identify the nature, site and extent of antigen modification and the results have been correlated with the accessibility of these residues in the native protein. Results for peptide models have shown that sulphur-containing and aromatic amino acids are modified preferentially. The extent of modification at these sites provides a measure of solvent accessibility in the vicinity of these residues.