Intrinsic disorder in proteins: a challenge for UNstructural biology met by ion mobility mass spectrometry

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A common approach to understanding protein function is to ‘solve’ its structure and subsequently probe interactions between the protein and its binding partners. The first part of this approach is non-trivial for intrinsically or inherently disordered proteins (IDP’s) which constitute up to 40% of all expressed proteins, and a much higher percentage in proteins involved in the proliferation of Cancer. Here we use ion mobility mass spectrometry to assess the relative disorder of wild type p53 and mutants of the DNA binding domain.

The p53 protein is a transcription factor which plays a central role to tumour suppression. Mass spectrometry studies of WT p53 and mutants following nano-electrospray from native conditions show a wide charge state range for monomeric species. The collision cross-sections of the monomer are observed to increase with increasing charge in a stochastic fashion attributed to protein unfolding due principally to Coulombic repulsion, which can be attributed to the ‘plasticity’ of these IDP’s. Multiple gas-phase conformers are resolved for a number of charge states, over a very wide charge state range. The thermally induced unfolding also shows interesting trends, and in particular reveals the resistance to unfolding of this important IDP. These results are interpreted in terms of the biological activity of these proteins and also in terms of the implications for the use of IM-MS to study this largely ignored but critically important class of proteins.