The work of Puglisi et al. deals with the observation of protein thermal denaturation processes occurring at low and high temperatures with the very interesting model of Yfh1.

The authors stress the merits of 2D HSQC spectra in addressing the denaturation processes at the single-residue resolution level. This approach can surely shed light into the characteristics of the unfolding/folding transitions that may be more complex than the general all-or-none model. However the main point the authors stress, i.e. the bipartite behavior of locally structured and unstructured residues of the protein with respect to the denaturation transitions, appears really paradoxical, as the same authors point out.

The intensity or volume change of the amide resonances with temperature may well indicate an unfolding transition, but may also report different processes. It may be conceivable that flexible regions of the protein could locally anticipate the unfolding transition obtained by heating the protein, thereby providing evidence in favor of a redefinition of the all-or-none model. However it is difficult to imagine a protein exoskeleton of flexible or even locally unstructured residues that undergo the cold denaturation transition at lower temperatures with respect to the collapse of the main core. Which would be the driving forces for this "resilience", as the authors define the scenario? The authors do not provide any independent evidence supporting their interpretation. In my opinion, the lower temperature of the flexible or unstructured residue "transitions" could be interpreted as progressively slowing-down local exchange processes that eventually reach the intermediate exchange regime. These processes seem quite uncorrelated if one considers the spread of the curves in Figure 1d. The authors should at least rule out the possibility of local conformational exchange taking place in the statistically-disordered unfolded state that is achieved at Tc.

The manuscript should be profoundly modified to be accepted for publication.