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Folding Stability of Yb1- Cold Shock Domain Inside Cells and Its Modulation by Ligand Binding

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YB1 is an intrinsically disordered protein with a conserved structural DNA/RNA binding domain (cold shock domain (CSD)) crucial for translation, transcription, and RNA metabolism, positioning it as a key therapeutic target against cancer and HIV. Its functions often require interactions between the CSD and nucleic acids. In vitro, CSD is marginally stable, however, the consequences of this on its cellular function are not fully understood. Our study focuses on determining the folding stability of CSD in a living cell at the physiological levels of nucleic acids. Our results suggested that CSD (CSD129), when extended by a disordered C11-tail (CSD140), is more stable than the conserved CSD129, with both proteins being significantly unfolded at physiological conditions. Nevertheless, in vitro experiments illustrated that the stability is enhanced upon addition of nucleic acids, more pronounced for RNA than DNA, in a sequence-dependent manner. Both our thermodynamic and kinetic analyses showed the presence of conformational diversity in the CSD native ensemble. We suggest this conformational diversity allows efficient binding to various ligands, however, at a cost of folding stability. Hence, we proposed that the marginal stability of the protein is required for efficient binding to different ligands, supporting its multifunctional.