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**Forced unfolding of proteins within cells – a proteomic method**

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— Many cellular activities are mediated by conformational changes in proteins or else involve rearrangement of protein assemblies. These motions are now commonly investigated in vitro as well as at the single-molecule level. But we sought to develop an in-cell method to study these motions and to do so on a proteomic scale. We have been especially interested in studying molecular responses in cells under stress, and we initially developed a labeling technique in the simplest human cell, the red blood cell. The premise is to label cysteines with cell-viable, thiol-reactive fluorophores in both stressed and unstressed cells. Then, differential labeling of proteins would indicate that under stress, previously buried cysteine residues become exposed and thus accessible to the fluorescent probe. Fluorescence imaging and saparations provide initial clues to structures and proteins, but Mass Spectrometry precisely maps the sites that are exposed. Subsequent work on recombinants and in modeling is then used to explain the cell-derived findings, and the method has now been applied to several nucleated cell types.

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