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► **COVER:** 'Filament bundles' by Vicky Askew, inspired by the Review on p562



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It's likely that you are taking a break from the daily stresses and relaxing in a comfy chair while reading this month's issue. Cells, like whole organisms, are also subjected to different stresses and have developed ways to cope. Mechanical stress, for example, can be caused by physiological processes such as digestion, muscle movements and breathing. Harald Herrmann and colleagues (page 562) discuss how intermediate filaments (IFs) form flexible matrices throughout the nucleus and cytoplasm that absorb mechanical stress, stabilize cell shape and function synergistically with other cytoskeletal networks. IFs are assembled from a large family of cell-type-specific proteins with different nanomechanical properties. The characterization of disease mutations in human IF proteins indicates that the nanomechanical properties of cell-type-specific IFs are central to the pathogenesis of various diseases, including muscular dystrophies and premature-ageing disorders. So, understanding how these mutations lead to changes in the cellular architecture could potentially result in therapeutic approaches.

Cells are often faced with other forms of stress, such as a build-up of unfolded proteins in the secretory pathway — so-called endoplasmic reticulum (ER) stress. Unfolded proteins have a tendency to aggregate or misfold and can thereby become toxic to cells. On page 519, David Ron and Peter Walter describe how cells cope with ER stress through the presence of three separate sensors, or stress receptors, in the ER membrane. Following detection of accumulated unfolded proteins in the ER lumen, these receptors activate the unfolded protein response (UPR). The UPR then orchestrates a remodelling of the ER that accommodates and reduces the unfolded protein load — thereby lessening cellular stress levels and keeping cells healthy.

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