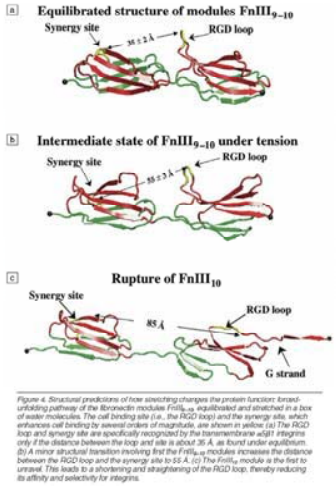
Molecular switches in the cell: fibronectin as a mechanical switch (Vogel, 2002)

- Fibronectin is an adhesion protein secreted by cells and assembled into fibrils to support adhesion and migration
- Composed of 'modules' of fibronectin repeats FnI, FnII, and FnIII connected by short linkers of varying flexibility
- One particular FnIII repeat, $FnIII_{10}$, contains the RGD amino acid sequence
- FnIII modules have interesting force-responsive properties
    - undergo partial unfolding in response to physiological forces (Figure shows stretched FN repeats in fibrillar FN)
        - integrins bind to and pull on FN fibers through the cytoskeleton
    - Several potential roles for this sensitivity:
        - Expose buried recognition sites
            - So-called 'cryptic' sites in $FnIII_1$, $FnIII_{7\text{-}8}$, $FnIII_{10}$, and $FnIIII_{14}$
        - Change relative distance between synergistic binding sites on 2 different modules
            - E.g. RGD synergy site between $FnIII_9$ and $FnIII_{10}$
        - Mechanical deformation and straightening of recognition sites on loops

Structure of fibronectin



(Vogel, 2002)

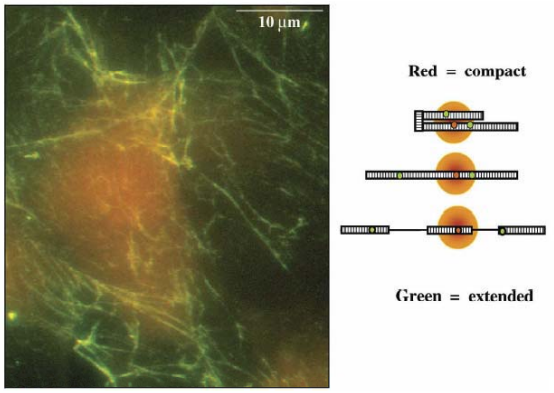


Figure 3. Translating structural changes within a protein into color changes. Fluorescence resonance energy transfer (FRET) is used to image different coexisting structural states of the adhesion protein fibronectin in a cell culture. The fibronectin was labeled randomly with donors (Oregon green) and site-specifically with acceptors (tetramethyl rhodamine) on the modules $FnIII_7$ and $FnIII_{15}$. The illustration to the right shows how FRET between donor (green) and acceptor (red) fluorophores is reduced upon protein unfolding (denaturing), as the protein structure changes from compact to extended to partially unfolded if mechanically stretched. The large sphere gives the range over which FRET can occur (<10 nm). Fibronectin is in a compact state if diffusely adsorbed to the cell surface, resulting in high-energy transfer, seen as red in the micrograph. The cells assemble fibronectin into fibrils that show far less energy transfer and are therefore green in the micrograph. A spectroscopic analysis further reveals that fibronectin is extended and partially unfolded in the matrix fibrils (green).[44]

Other examples of molecular switches in biology

Adhesin adhesion protein in E. Coli:

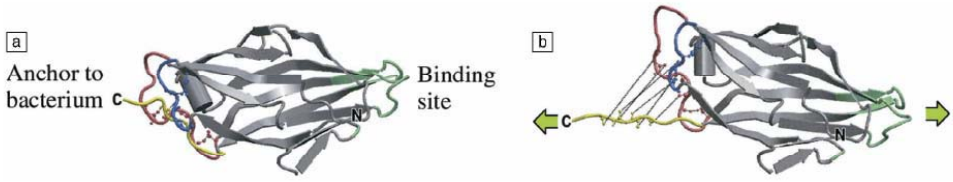


Figure 2. A mechanochemical nanoswitch. The bacterial adhesin FimH, which allows E. coli *to specifically bind to target cells, switches from low to high affinity if mechanically stretched by shear force acting on the protein. The binding site is shown in green, and the receptor C strand that connects the module to the rest of the bacterium is shown in yellow. The structure in (a) has been equilibrated, surrounded by water molecules (not shown). Mechanical stretching, symbolized by green arrows in (b), leads to the breakage of a cluster of six backbone hydrogen bonds between the yellow β strand and the two loop regions shown in red and blue. The structural perturbation induced by the pull-out of the yellow β strand presumably propagates through the protein to the binding site, triggering the switch to high affinity.[37]*