Life Sciences Seminar

Structural insights into stress sensing mechanisms in the endoplasmic reticulum

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To adjust the folding capacity of the endoplasmic reticulum (ER), cells rely on the unfolded protein response (UPR), a signaling network that relays the ER folding status to the nucleus via ER-resident sensors. IRE1 is the most conserved sensor and is found from yeast to human. How IRE1 senses ER-stress remained elusive. Early models suggested that the ER-resident chaperone BiP to be the sole regulator of IRE1 activity. We recently showed that IRE1s sensor domain recognizes unfolded polypeptides accumulating in the ER as direct ligands. Using nuclear magnetic resonance (NMR) spectroscopy experiments, we found that unfolded proteins bind to the MHC-like fold in the human IRE1 lumenal domain (LD) and induce a conformational change in a distant helix that promotes its oligomerization. Instead, the NMR approaches revealed that the ER-resident chaperone BiP binds to a distinct site at the periphery of IRE1 LD dimers and modulates its oligomerization. Our results support the model that unfolded protein binding activates IRE1 directly and a non-canonical chaperone binding buffers IRE1 activity.

Wednesday, November 6, 2019 11:30am - 12:30pm

Mondi Seminar Room 2, Central Building

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