BIOCHEMISTRY SEMINAR

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"Activation of the Ubiquitin Ligase by a Molecular Glue"

Abstract:

Mutations in parkin cause an early-onset form of Parkinson's disease (PD). Parkin is a ubiquitin ligase that is recruited to damaged mitochondria to target them for degradation. Upon phosphorylation by PINK1, parkin undergoes a large conformational change to release ubiquitin ligase activity. Recent studies have discovered a class of small molecules that can activate parkin without phosphorylation. The compounds act as molecular glues and enhance the affinity of phospho-ubiquitin binding to parkin by over 2000-fold. A crystal structure shows the compounds bind next to phospho-ubiquitin on the parkin RING0 domain, promoting the displacement of the ligase catalytic domain via an alternative, feed-forward activation pathway. *In organello* and mitophagy assays show that the compound rescues the activity of two PD mutations, R42P and V56E. The compounds provide the basis for the design of first therapeutics to stop the progression of PD.

Biography:

Kalle Gehring trained at Brown University, the University of Michigan, and the University of California at Berkeley (PhD, Microbiology). As a postdoctoral fellow at the Ecole Polytechnique in France, he used NMR spectroscopy to determine the first four-stranded i-motif (intercalated) DNA structure. Since joining McGill University as an Assistant Professor in 1994, he has been active leading grants for equipment and training in structural biology and biophysics. His research group in Montreal works on parkin, a ubiquitin ligase that protects against Parkinson's disease, and a recently discovered signaling pathway involving cysteine phosphorylation. Lab website: www.gehringlab.net