Shape Shifting in Apoptosis-Inducing Factor Allostery and Interactions: Switching between Oxidative Phosphorylation and Cell Death

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Ligand-driven conformations of Apoptosis-Inducing Factor (AIF) dictate functional assemblies that switch from maintenance of mitochondrial oxidative phosphorylation and to signaling caspase independent cell death. At mitochondrial cell membrane sites distant from damaged DNA, AIF links DNA damage signaling and repair pathways to the cell's metabolic state to facilitate recovery of genomic integrity or to initiate cell death. Hyperactivation of the break repair and signaling enzyme poly(ADP-ribose) polymerase-1 (PARP-1) induces consumption of NAD+ and induction of necroptotic cell death ('parthanatos') via the mitochondrial release and nuclear accumulation of AIF. We hypothesize that allosteric switching of AIF subunit architecture by NADH regulates this transition. By integrating data from small-angle X-ray scattering (SAXS), X-ray crystallography, and computation, we are examining shape-shifting mechanisms linking AIF's NADH active site to allosteric rearrangements that create a functional dimerization surface including the release of a 50-residue loop. As part of these efforts, we are investigating the AIF's mitochondrial binding partners, higher-order oligomerization of AIF, and their implications for allosteric sensing of NAD(H). A molecular-based knowledge of AIF allostery will enable mechanistic insights linking mitochondrial homeostasis, cellular metabolism, DNA damage signaling, and cell death.