Enzyme Active Site Loop Revealed as Gatekeeper for Cofactor Flip by Targeted Molecular Dynamics Simulations and FRET-kinetics
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**The context**

Aldehyde dehydrogenases: NAD(P)-dependent dehydrogenases
Involved in detoxication and metabolic pathways (retinoic acid biosynthesis)

**The question**

Reduced nicotinamide moiety (NMNH) flipping is required for Glu-268 to activate the water molecule in the decylation step

**The strategy**

Reduced nicotinamide moiety (NMNH) flipping

Impact on catalysis?

→ Kinetic approach

→ Intrinsic Trp/NADH FRET probe

Driving force?

→ Identification of molecular factors allowing cofactor movement

→ Targeted Molecular Dynamics

**Conserved ELGG as a gatekeeper for cofactor flipping**

**Targeted Molecular Dynamics: GAPN**

**Rapid kinetic monitoring of the flip using stopped flow**

**Enzyme Active Site Loop Revealed as Gatekeeper for Cofactor Flip by Targeted Molecular Dynamics Simulations and FRET-kinetics**

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**References**


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**CONCLUSION**

- Flip/catalytic efficiency relies on ELGG loop flexibility
- Cofactor flipping extends to all ALDH family including CoA-dependent aldehyde dehydrogenases