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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 detoxification and metabolic pathways (retinoic acid biosynthesis)

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

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

NMNH conformation monitoring by FRET
RALDH2

Rapid kinetic monitoring of the flip using stopped flow

G271A mutation in ELGG loop drastically reduces the flip kinetics

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

References
Rahuel-Clermont, S., Bchini, R., Barbe, S., Boudewijn, S., André, I., and Talfournier, F. (2019) Enzyme Active Site Loop Revealed as a Gatekeeper for Cofactor Flip by Targeted Molecular Dynamics Simulations and FRET-Based Kinetics. ACS Catal. 9, 1327-1346