An Enzymatically Switchable Sink in the Rod Inner Segments: A Model for Slow Return of Transducin to the Outer Segments

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Purpose: UNC119 (UNC119HRG4), a homolog of C. elegans UNC-119, is a protein with sequence similarity to PrBP. UNC-119 is ubiquitously expressed in multiple tissue in all animals tested, and abnormally in photoreceptors in mice carrying the inner segment syndrome. We previously identified UNC-119 as a novel acyl-binding protein with specificity for the transducin alpha subunit (Tα). The purpose of this study is to study interaction of UNC-119 with Tα.

Results: Isothermal titration microcalorimetry of UNC119 with an acylated N-terminal peptide of Tα shows tight interaction (Kd = 0.3 µM). Reconstitution of purified Tα with depleted ROS membranes and UNC-119 shows the ROS-to-granule GDP/GTP exchange of Tα. Co-crystallization of UNC-119 with the acylated Tα peptide reveals that the lipid chain is buried deeply into UNC-119 hydrophobic cavity formed by an immunoglobulin-like (Ig) fold motif. The cavity is crucial for Tα binding and for hydrophobic residues nearby. Ile and Tyr that enable interaction with the acylated lipid chain.

Conclusions: We propose a model for the return of transducin to the outer segment by diffusion. The enzymatically switchable sink interacts with the inner segment in the absence of GDP (phosphatase) and is a rate-limiting step in return of transducin to the outer segments.

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