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Critical roles for intracellular binding proteins in creating a robust retinoic acid morphogen gradient

Retinoic acid (RA) is a vitamin A derivative that acts as a graded morphogen to promote posterior cell fates in the vertebrate central nervous system (CNS). CNS development occurs normally over a 20-fold range of RA concentrations, indicating a remarkable degree of gradient robustness.

Cellular retinoic acid binding proteins (Crabps) transport RA intracellularly but their roles in morphogen gradient formation remain unclear. Using a combination of computational and experimental approaches in zebrafish, we show that both positive and negative feedback by Crabps on RA signaling dramatically improves robustness. Crabps improve robustness within an optimal concentration range and transport of Crabp bound RA to Cyp26 degradation enzymes appears to be critical for these robustness gains. These results suggest that Crabps are essential for modulating the RA signaling gradient in the face of varying levels of dietary vitamin A.