

Glia-derived Insulin-like Peptides Regulate the Timing of Photoreceptor Differentiation in the *Drosophila* Visual System

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Abstract

Recent studies suggest the involvement of insulin signaling in the timing of photoreceptor differentiation in *Drosophila* and mammals. The molecular and cellular mechanisms underlying temporal control of photoreceptor differentiation by insulin signaling, however, remain largely undefined. In this study, we reveal a key role for sub-retinal glia in timing the differentiation of photoreceptor neurons (R cells) in the developing *Drosophila* eye imaginal disc. Decreasing the signaling of epidermal growth factor receptor (EGFR) in sub-retinal glia delayed R-cell differentiation. In contrast, hyperactivating the EGFR pathway in sub-retinal glia caused the precocious R-cell differentiation. Cell-type-specific knockdown, epistasis analysis and transgene rescue indicate that insulin-like peptides ILP3 and ILP6 are key downstream targets of the EGFR pathway in sub-retinal glia. Our results support that the activation of the EGFR pathway in sub-retinal glia stimulates the release of ILP3 and ILP6, which in turn activate the insulin receptor (InR) in eye precursor cells to positively regulate the timing of photoreceptor differentiation. To our knowledge, this is the first study that reveals the cellular source and the identity of insulin-like family members that act *in vivo* to regulate the timing of photoreceptor differentiation in both vertebrates and invertebrates.

Keywords

Insulin-like Peptides, Ilp, Photoreceptor, Glia, Differentiation, *Drosophila*