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Ras signaling in *Drosophila*oogenesis

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Abstract

Dorsoventral patterning in *Drosophila* oogenesis reveals new links between *Ras1* and genes involved in signaling and cytoskeletal organization

Significance and context

Ras1 is the *Drosophila* homolog of the mammalian transforming genes Ha-*Ras*, Ki-*Ras* and N-*Ras*. In mammals the Ras superfamily of GTPases is larger than in *Drosophila* - there are around 19 members, which represent some 20% of the superfamily of small GTP-binding-proteins. These proteins are known to act as molecular switches that transduce upstream signals to downstream effectors. Mutation of the three human *Ras* genes has been seen in some 30% of all human cancers, and many further cancer-related signaling pathways have been shown to involve aberrant Ras function. Through a genetic analysis of the much simpler Ras1 signaling pathway in *Drosophila*, Schnorr *et al.* have identified new signaling and cytoskeletal interactions that should provide information on the function of their mammalian counterparts.

Key results

Using a dominant modifier screen in *Drosophila*, the authors have identified genes that enhance a weak *Ras1* aberrant phenotype during oogenesis. Three of these mutant '*Ras1 Enhancers*' represent known proteins involved in Ras1 signaling pathways in *Drosophila*: the EGF receptor (Egfr); Star, a single-pass transmembrane protein that is required for EGF signaling; and Blistered, a transcription factor that is dependent on the function of the receptor tyrosine kinases Breathless and Egfr. Seven other identified genes encode proteins involved in cell signaling and the regulation of the cytoskeleton, but which have not been linked to this Ras1 pathway before: Chickadee, Tec29, Dreadlocks, POSH, Peanut, Smt3 and MESK2. Of the two remaining *Ras1 Enhancers*, one maps to an overlapping region containing genes for a putative receptor tyrosine kinase, Nrk, and a protein that is thought to be involved in the degradation of neuropeptides, TppII. The final one lies within four candidate genes, one showing homology with the Notch and Delta family of cell adhesion molecules, and the other three encoding proteins of no known function. Schnorr *et al*. have also identified five lines with the *Ras1 Enhancer* phenotypethat are independent of the *Ras1* mutation, and instead involve the *Sec61β* gene, which codes for a putative protein translocation channel.

Methodological innovations

With the help of the Berkeley *Drosophila* Genome Project (BDGP), Schnorr *et al.* have combined the standard technique of genetically-engineered P transposable elements inserted in genomic regions with the generation of a weak *Ras1* allele that provides a threshold for adequate signaling through this pathway. The extent of the *Ras1* phenotype was assessed by studying defects in eggshell formation. They conducted a breeding scheme to introduce these mutations into the weak *Ras1* background, followed by a genetic screen to find heterozygous mutations that enhanced the phenotype - the *Ras1 Enhancers*.

Reporter's comments

This is essentially a study of the functions that can be linked to the *Ras1 Enhancer* genes (and hence their protein products) in *Drosophila*. Initially, identification of two known Ras1 pathway components in oogenesis - *Egfr* and *Star* - as *Ras1 Enhancers* demonstrates the efficacy and suitability of Schnorr and colleagues' approach. The *Blistered* gene is also known to be part of the Ras1 signaling pathway, although its previously demonstrated function in wing development indicates a different form of regulation from that described here. In addition to these known interactions, this study identifies other potential *Ras1* interactors in dorsoventral patterning in *Drosophila* oogenesis. Thus, Dreadlocks, Tec29 and POSH are revealed as new members of this Egfr/Ras1-regulated developmental pathway. At the same time, and in conjunction with Chickadee, Peanut and Smt3, they are also now seen to be involved in the regulation of the cytoskeleton, which itself is shown to be crucial in *Drosophila* oogenesis.

A further benefit of this work is its potential bidirectionality - the mammalian system can indicate functions of the *Drosophila Ras1 Enhancers* and *vice versa*. The mammalian homologs of POSH, Chickadee and Peanut have previously been implicated in cytoskeletal reorganization, and this study confirms these interactions. Similarly, the mammalian counterpart of Nck is known to interact with Sos, an interaction that has not previously been shown for the *Drosophila* Nck homolog, Dreadlocks, which has instead been linked to Misshapen and Pak through neuronal development. These points are also discussed in further detail by the authors.

Certain questions remain that will help to identify further interactors of both *Drosophila* and mammalian proteins. Is *Nrk* or *TppII* the true *Ras1 Enhancer* (the authors provide arguments for both), and what of the two novel genes identified in this system? Finally, although Schnorr *et al*. have used the ability to suppress activated Egfr to show that Dreadlocks and Smt3 operate downstream of Egfr, the full profile of the involvement of the remainder of the *Ras1 Enhancers* in this, and other, Ras1 signaling pathways still needs to be determined.

Table of links

References

1. Schnorr JD, Holdcraft R, Chevalier B, Berg CA: *Ras1* interacts with multiple new signaling and cytoskeletal loci in *Drosophila* eggshell patterning and morphogenesis. Genetics. 2001, 159: 609-622. 0016-6731