MECHANISMS OF DEVELOPMENT 129 (2012) 339–349

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Regulation of Yorkie activity in *Drosophila* imaginal discs by the Hedgehog receptor gene *patched*

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ARTICLE INFO

Article history:
Received 3 February 2012
Received in revised form
6 May 2012
Accepted 10 May 2012
Available online 15 June 2012

Keywords:
Patched
Hedgehog
Apoptosis
Yorkie
Growth
Drosophila

ABSTRACT

The Hedgehog (Hh) pathway was first defined by its role in segment polarity in the *Drosophila melanogaster* embryonic epidermis and has since been linked to many aspects of vertebrate development and disease. In humans, mutation of the *Patched1* (*PTCH1*) gene, which encodes an inhibitor of Hh signaling, leads to tumors of the skin and pediatric brain. Despite the high level of conservation between the vertebrate and invertebrate Hh pathways, studies in *Drosophila* have yet to find direct evidence that *ptc* limits organ size. Here we report identification of *Drosophila ptc* in a screen for mutations that require a synergistic apoptotic block in order to drive overgrowth. Developing imaginal discs containing clones of *ptc* mutant cells immortalized by the concurrent loss of the *Apaf-1-related killer* (*Ark*) gene are overgrown due, in large part, to the overgrowth of wild type portions of these discs. This phenotype correlates with overexpression of the morphogen Dpp in *ptc,Ark* double-mutant cells, leading to elevated phosphorylation of the Dpp pathway effector Mad (p-Mad) in cells surrounding *ptc,Ark* mutant clones. p-Mad functions with the Hippo pathway oncoprotein Yorkie (Yki) to induce expression of the pro-growth/anti-apoptotic microRNA *bantam*. Accordingly, Yki activity is elevated among wild type cells surrounding *ptc,Ark* clones and alleles of *bantam* and *yki* dominantly suppress the enlarged-disc phenotype produced by loss of *ptc*. These data suggest that *ptc* can regulate Yki in a non-cell autonomous manner and reveal an intercellular link between the Hh and Hippo pathways that may contribute to growth-regulatory properties of the Hh pathway in development and disease.

1. Introduction

Genetic screens in the fruit fly *Drosophila melanogaster* have identified a number of genes that are required to restrict the growth of developing tissues (reviewed in Hariharan and Bilder (2006); Pan (2007)). A number of these genes control the process of tissue growth by regulating largely cell-intrinsic mechanisms that modulate rates of cell division, death, or growth. However, other genes exhibit more complex phenotypes indicative of roles in intercellular signaling and morphogen-based pathways that pattern the growth and differentiation of groups of cells in developing organs. Vertebrate orthologs of both classes of *Drosophila* anti-growth genes are mutated in human disease and collaborate with anti-apoptotic mutations to drive cancer (e.g. Hanahan and Weinberg, 2011; Vidal and Cagan, 2006). Similar synergy occurs in *Drosophila* (Asano et al., 1996; Herz et al., 2006; Nicholson et al., 2009; Staehling-Hampton et al., 1999) and has been used to identify 'conditional' pro-growth mutations

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0925-4773/$ - see front matter © 2012 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mod.2012.05.007

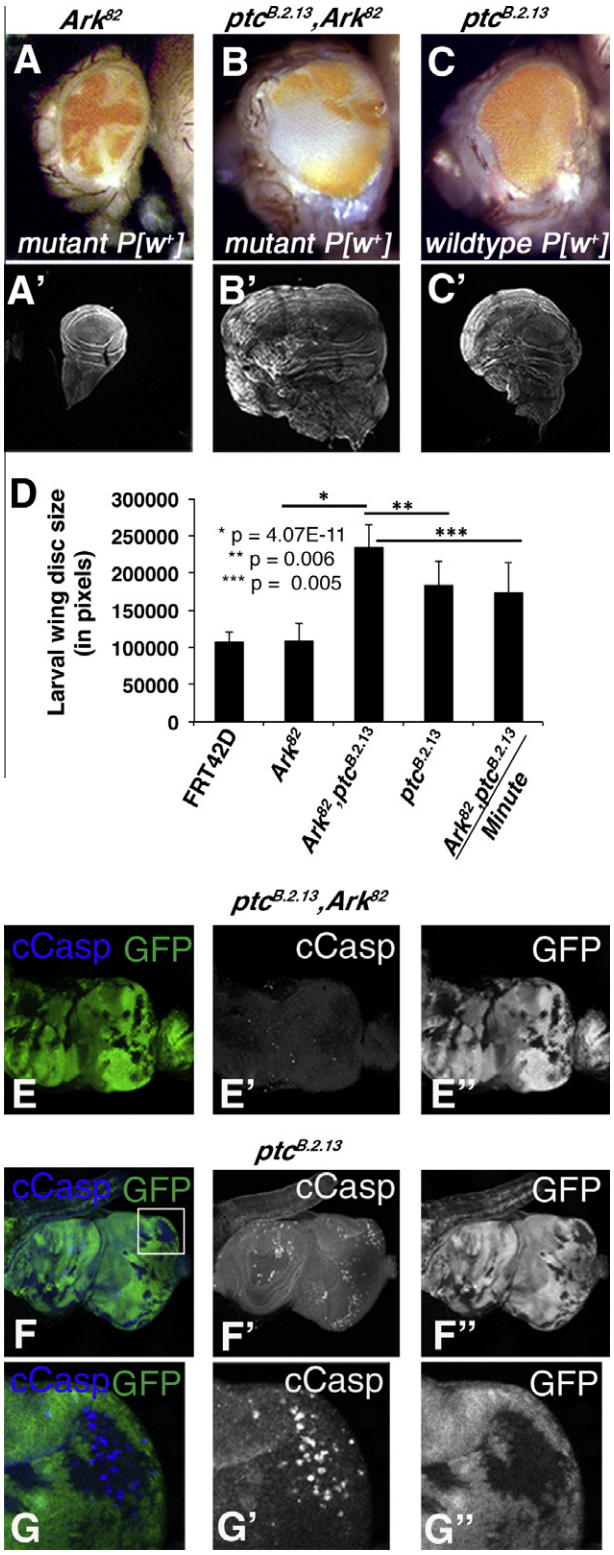

Fig. 1 – A mosaic screen for conditional suppressors of growth identifies a novel allele of *patched*, $ptc^{B.2.13}$, as a conditional suppressor of growth. Mosaic adult eyes and imaginal wing discs from L3 larvae, stained with phalloidin: (A and A′) Ark^{82} (mutant tissue is pigmented) (B and B′) $ptc^{B.2.13}$,Ark^{82} (mutant tissue is pigmented) (C and C′) $ptc^{B.2.13}$ (wild type tissue is pigmented);(D) quantification of mosaic wing discs size from L3 larvae demonstrates the conditional nature of the $ptc^{B.2.13}$,Ark^{82} overgrowth; mosaic larval eye discs stained with anti-Cleaved Caspase 3 (cCasp) shows $ptc^{B.2.13}$ mutant clones accumulate cCasp without Ark^{82}(E and E″) $ptc^{B.2.13}$,Ark^{82} (mutant tissue is GFP negative)(F and G″) $ptc^{B.2.13}$ (inset is amplified in G and G″) (mutant tissue is GFP negative).