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## Data Article

# Local overexpression of Su(H)-MAPK variants affects Notch target gene expression and adult phenotypes in *Drosophila*

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## ABSTRACT

In *Drosophila*, Notch and EGFR signalling pathways are closely intertwined. Their relationship is mostly antagonistic, and may in part be based on the phosphorylation of the Notch signal transducer Suppressor of Hairless [Su(H)] by MAPK. Su(H) is a transcription factor that together with several cofactors regulates the expression of Notch target genes.

Here we address the consequences of a local induction of three *Su(H)* variants on Notch target gene expression. To this end, wild-type *Su(H)*, a phospho-deficient *Su(H)<sup>MAPK-ko</sup>* and a phosphomimetic *Su(H)<sup>MAPK-ac</sup>* isoform were overexpressed in the central domain of the wing anlagen. The expression of the Notch target genes *cut*, *wingless*, *E(spl)m8-HLH* and *vestigial*, was monitored. For the latter two, reporter genes were used (*E(spl)m8-lacZ*, *vg<sup>BE</sup>-lacZ*). In general, *Su(H)<sup>MAPK-ko</sup>* induced a stronger response than wild-type *Su(H)*, whereas the response to *Su(H)<sup>MAPK-ac</sup>* was very weak. Notch target genes *cut*, *wingless* and *vg<sup>BE</sup>-lacZ* were ectopically activated, whereas *E(spl)m8-lacZ* was repressed by overexpression of *Su(H)* proteins. In addition, in epistasis experiments an activated form of the EGF-receptor (*DER<sup>act</sup>*) or the MAPK (*rl<sup>SEM</sup>*) and individual *Su(H)* variants were co-overexpressed locally, to compare the resultant phenotypes in adult flies (thorax, wings and eyes) as well as to assay the response of the Notch target gene *cut* in cell clones.

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## Specifications Table

Subject area	Biochemistry, Genetics and Molecular Biology
More specific subject area	Developmental Biology, Cellular signalling
Type of data	Figures and text
How data was acquired	Microscopy: Zeiss Axioskop linked to a Bio-Rad MRC1024 confocal microscope; Wild 5M stereomicroscope and Zeiss Axiophot coupled to an Optronics ES120 camera
Data format	Filtered data, analyzed
Experimental factors	Imaginal discs were dissected, fixed, washed and blocked before adding antibodies.
Experimental features	Tissue-specific expression of respective transgenes was induced with the Gal4::UAS-system. Gene expression was monitored directly or from reporter genes by antibody staining of the protein products.
Data source location	n.a.
Data accessibility	The data is with this article

## Value of the data

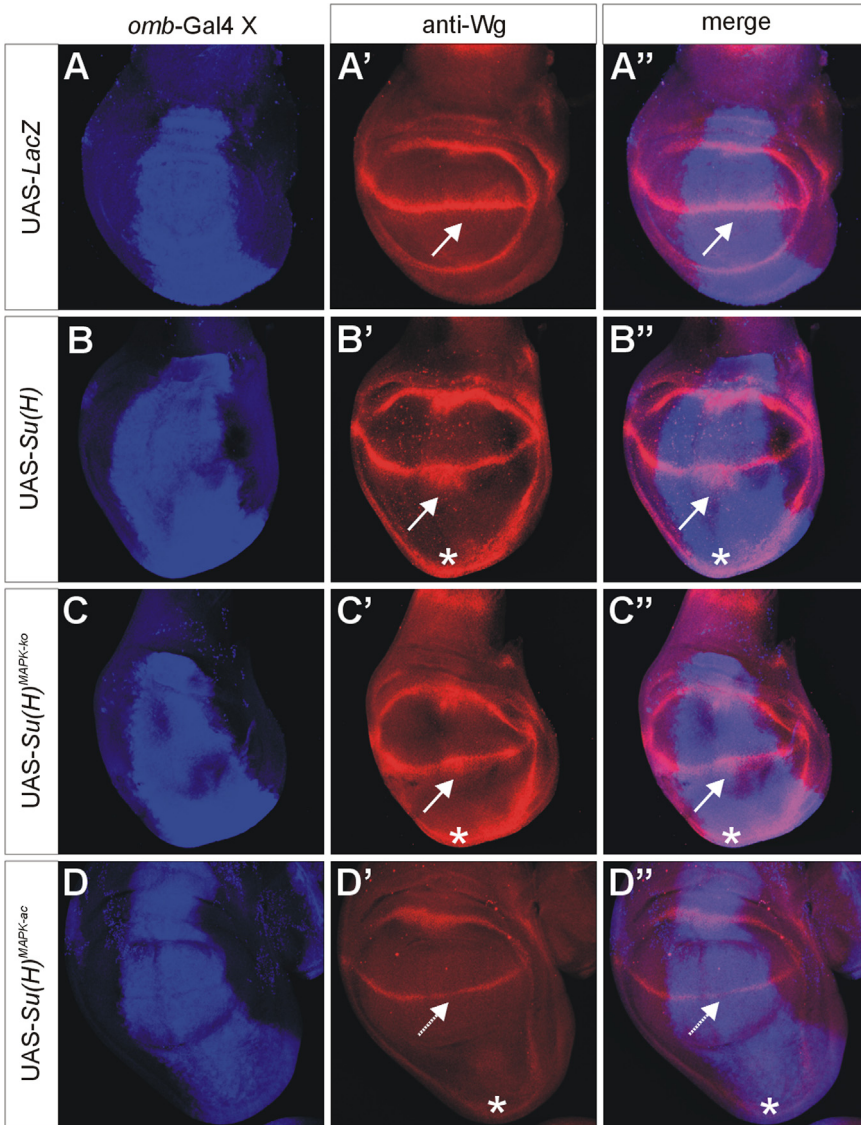
- This data shows the responses of several Notch target genes to modulations of Su(H) activity by the EGFR pathway.
- The data allow for a visual comparison of the spectrum of Notch target gene responses to Su(H) overexpression.
- Overexpression of activated components of the EGFR pathway and Su(H) variants, alone or in combination, can be compared in various *Drosophila* tissues.
- This data may be extended by analyses on *DER<sup>act</sup>* activity during *Drosophila* wing development.

## 1. Data

Suppressor of Hairless [Su(H)] is the transcription factor that regulates the expression of the target genes of the Notch signalling pathway [1,2]. Su(H) protein may be phosphorylated by MAPK as a result of Epidermal Growth Factor Receptor (EGFR) activation, providing a means of a direct cross-talk between these two pathways [3–5]. The response of several Notch target genes to the modulations of Su(H) by EGFR signalling activity was analysed by the local overexpression of either wild-type *Su(H)*, a phospho-deficient *Su(H)<sup>MAPK-ko</sup>* and a phospho-mimetic *Su(H)<sup>MAPK-ac</sup>* variant [3] using the Gal4::UAS system [6], and staining of the tissues with respective antibodies. Moreover, activated components of the EGFR pathway (*DER<sup>act</sup>*, *rt<sup>SEM</sup>*) were overexpressed alone or in combination with individual *Su(H)* variants. The response of the Notch target gene *cut* was observed in cell clones of wing imaginal discs, and the resultant phenotypes on thorax, wings and eyes were recorded in adult flies.

## 1.1. Overexpression of Su(H) variants during wing development

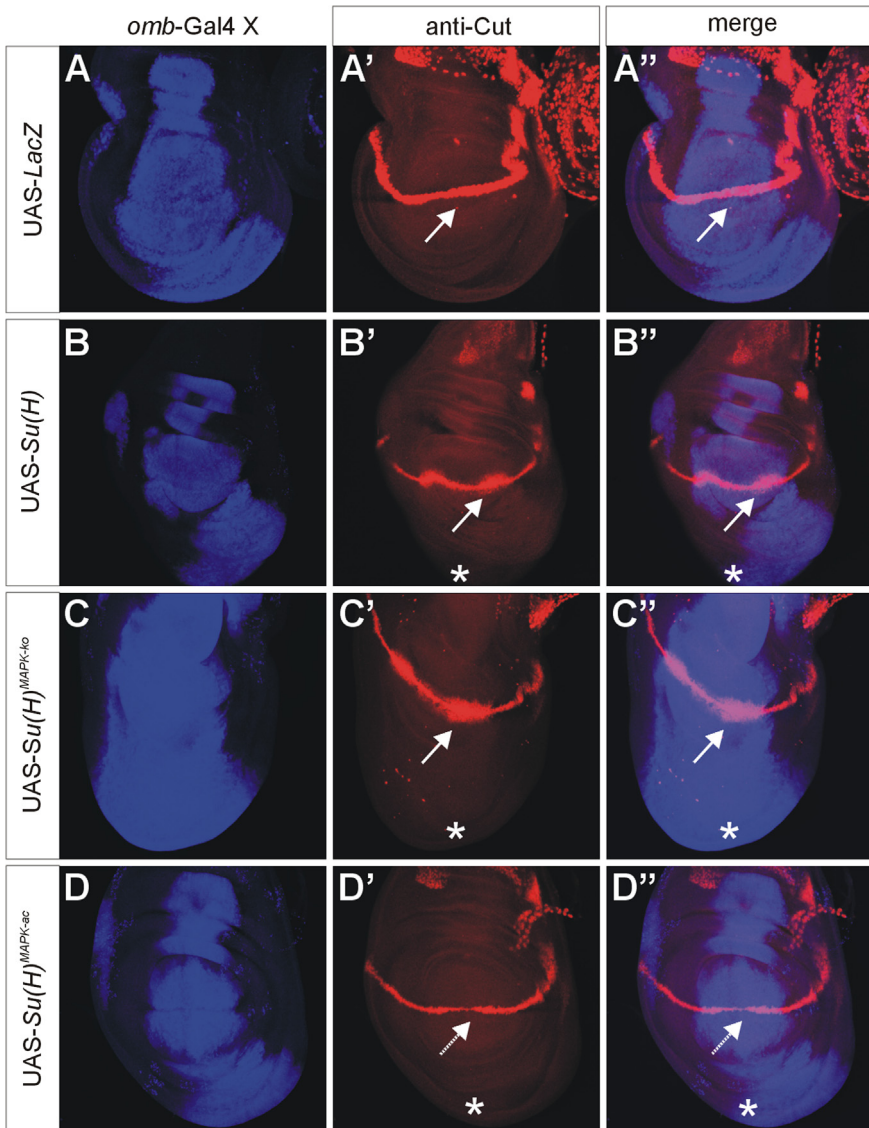
UAS-*Su(H)*, UAS-*Su(H)<sup>MAPK-ko</sup>* and UAS-*Su(H)<sup>MAPK-ac</sup>* were overexpressed with *omb*-Gal4 [7] in wing imaginal discs of third instar *Drosophila* larvae. A total of four Notch target genes was analysed, *wingless* (Fig. 1) [8], *cut* (Fig. 2) [9], *E(spl)m8-HLH* [10] (using *E(spl)m8-lacZ* [11], Fig. 3) and *vestigial* [12] (using *vg<sup>BE</sup>-lacZ* [13], Fig. 4). Overall, overexpression of *Su(H)<sup>MAPK-ko</sup>* caused a stronger response of the Notch target genes than that of wild-type *Su(H)*, whereas *Su(H)<sup>MAPK-ac</sup>* elicited the weakest effects, in agreement with a downregulation of *Su(H)* activity by MAPK-mediated phosphorylation [3].



**Fig. 1.** Response of the Notch target gene *wingless*. Overexpression of the UAS-*Su(H)* variants as indicated; the *omb*-expression domain is highlighted in blue in A–D and A'–D' (A, A' anti-beta galactosidase staining; B–D and B'–D', anti-*Su(H)* staining). Expression of *wingless* (*Wg*) is shown in red (A'–D'). UAS-*lacZ* served as control. Note expansion of *wingless* expression along the dorso-ventral boundary (arrows) upon overexpression of *Su(H)* and *Su(H)<sup>MAPK-ko</sup>*, but not *Su(H)<sup>MAPK-ac</sup>*. Overgrowth of the ventral disc is marked by asterisks and is a consequence of the overexpression of *Su(H)* protein (B'–D').

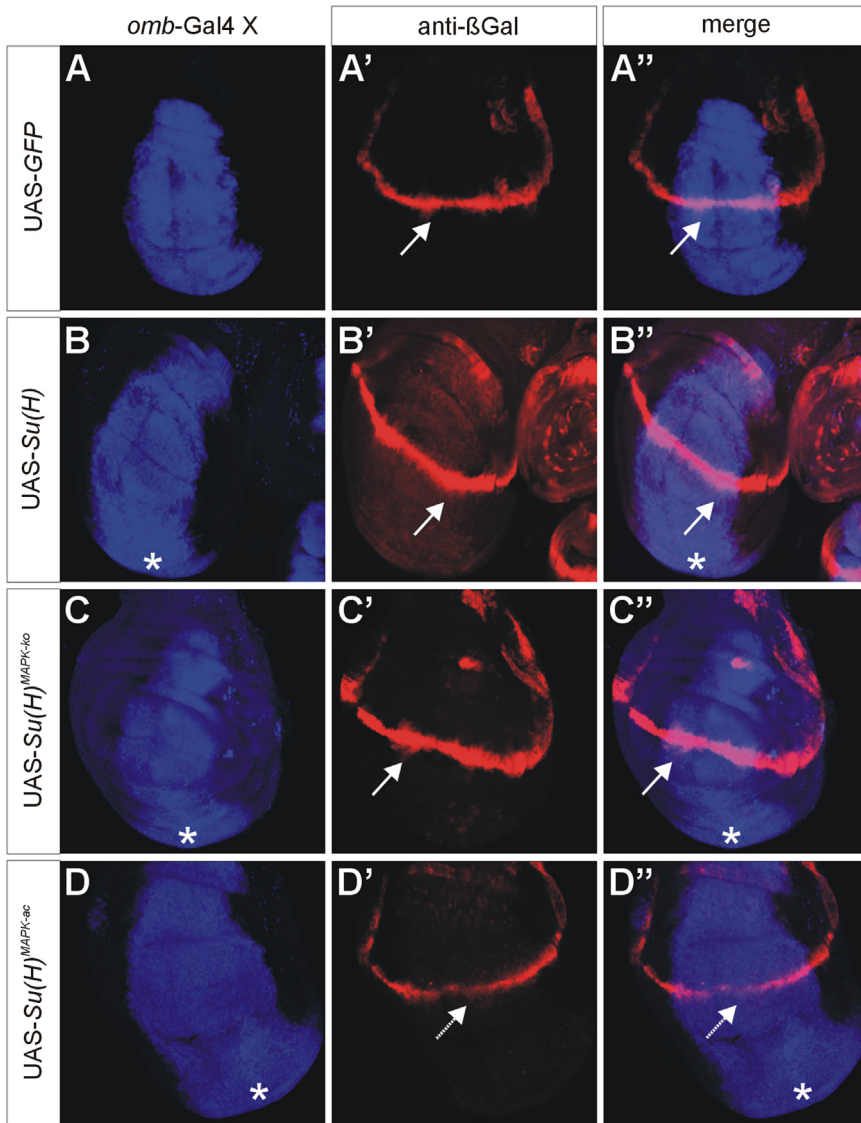
### 1.2. Response of *cut* expression to the combined induction of *Su(H)* variants and activated components of the EGFR pathway during wing development

The expression of the Notch target gene *cut* was analysed in cell clones overexpressing either of the three *Su(H)* isoforms alone or in combination with the activated EGF-receptor (*DER<sup>act</sup>*) or the activated MAPK (*rl<sup>SEM</sup>*) [14,15] (Fig. 5). Overexpression clones were induced in wing imaginal discs [16]. *Su(H)* overexpression induced *cut* expression, whereas it repressed it when simultaneously



**Fig. 2.** Response of the Notch target gene *cut*. Overexpression of the UAS-*Su(H)* variants as indicated; the *omb*-expression domain is highlighted in blue in A–D and A'–D' (A, A' anti-beta galactosidase staining; B–D and B'–D', anti-*Su(H)* staining). Expression of *cut* is shown in red (A'–D'). UAS-*lacZ* served as control. Note expansion of *cut* expression along the dorso-ventral boundary (arrows) upon overexpression of *Su(H)* and *Su(H)*<sup>MAPK-ko</sup>, but not *Su(H)*<sup>MAPK-ac</sup>. Overgrowth of the ventral disc is marked by asterisks and is a consequence of the overexpression of *Su(H)* protein (B'–D').

overexpressed with *r1*<sup>SEM</sup> (Fig. 5A–A'' and C–C'') [3]. Likewise repression was observed with *Su(H)*<sup>MAPK-ko</sup>, but less with *Su(H)*<sup>MAPK-ac</sup> (Fig. 5D and E''). Cell clones overexpressing *DER*<sup>act</sup> were frequently distorted, and *cut* expression was induced at the boundary of *DER*<sup>act</sup> expressing and non-expressing cells independent of the overexpression of any *Su(H)* variant (arrowheads in Fig. 5F'–I'').

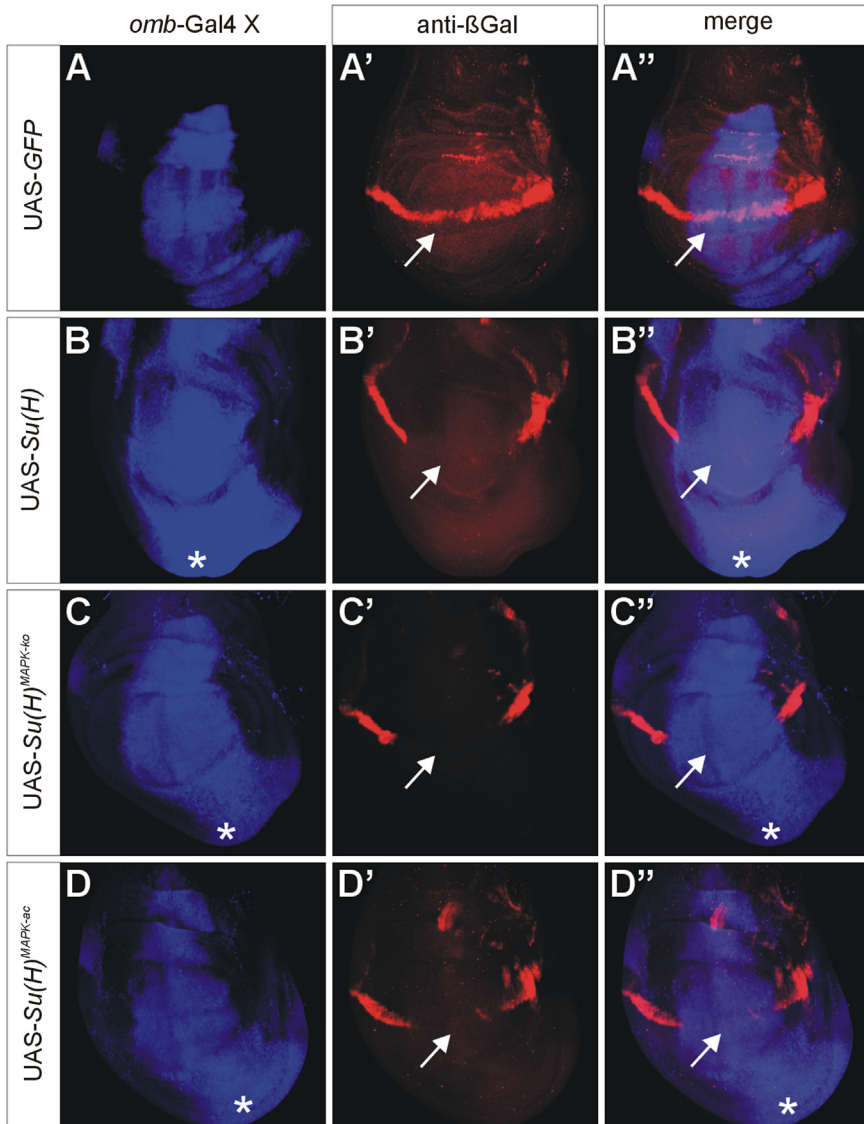


**Fig. 3.** Response of the Notch target gene *vestigial*. Overexpression of the UAS-*Su(H)* variants as indicated; the *omb*-expression domain is highlighted in blue in A–D and A'–D' (A, A' green fluorescent protein GFP; B–D and B'–D', anti-*Su(H)* staining). Expression of the *vestigial* reporter *vg<sup>BE</sup>-lacZ* is shown in red (A'–D'). UAS-GFP served as control. Note expansion of *vg<sup>BE</sup>-lacZ* expression along the dorso-ventral boundary (arrows) upon overexpression of *Su(H)* and *Su(H)<sup>MAPK-ko</sup>*, but not *Su(H)<sup>MAPK-ac</sup>*. Overgrowth of the ventral disc is marked by asterisks and is a consequence of the overexpression of *Su(H)* protein (B–D, B'–D').

### 1.3. Adult phenotypes resulting from the combined overexpression of *Su(H)* variants and activated components of the EGFR pathway

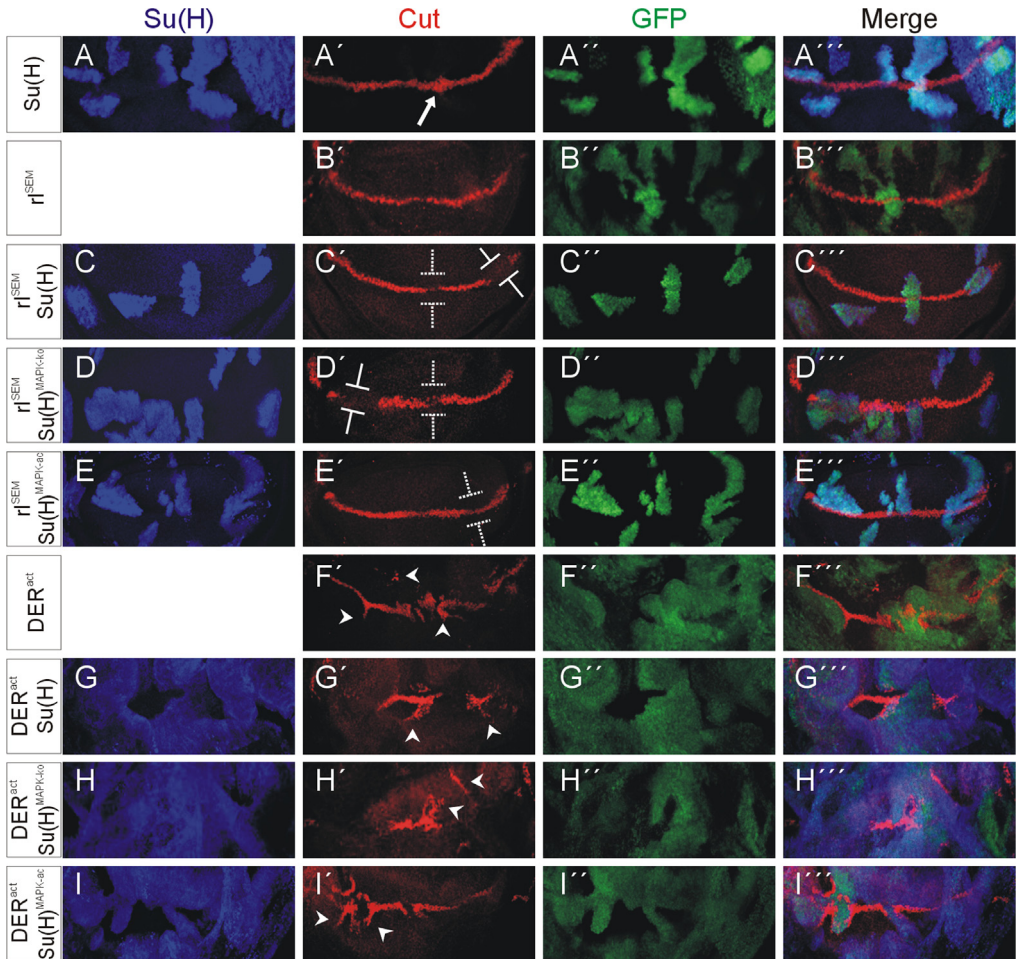
Overexpression of UAS-*DER<sup>act</sup>* in the thorax (Fig. 6) or the wing anlagen (Fig. 7A) using *Bx-Gal4* [17] was fully epistatic to the *Su(H)* gain of function phenotypes. This was in contrast to the simultaneous overexpression of UAS-*rt<sup>SEM</sup>* with the UAS-*Su(H)* isoforms: in these experiments the *Su(H)* gain of function phenotypes prevailed (Figs. 6 and 7B). It has been described before that the overexpression of *Su(H)* in the developing sensory organs using *sca-Gal4* causes a shaft to socket transformation [18],





**Fig. 4.** Response of the Notch target gene *E(spl)m8-HLH*. Overexpression of the UAS-*Su(H)* variants as indicated; the *omb*-expression domain is highlighted in blue in A–D and A'–D' (A, A' green fluorescent protein GFP; B–D and B'–D', anti-*Su(H)* staining). Expression of the *E(spl)m8-HLH* reporter *E(spl)m8-lacZ* is shown in red (A'–D'). UAS-GFP served as control. Note repression of *E(spl)m8-lacZ* along the dorso-ventral boundary (arrows) upon overexpression of the three *Su(H)* variants (B'–D''); overgrowth of the ventral disc is marked by asterisks (B–D, B''–D'').

which we also observed upon overexpression of *Su(H)<sup>MAPK-ko</sup>* or *Su(H)<sup>MAPK-ac</sup>* (Fig. 8). Whereas *sca::rl<sup>SEM</sup>* was similar to the control, *sca::DER<sup>act</sup>* animals developed tufts of macrochaetae on the posterior thorax (Fig. 8). Interestingly, in combination with any of the *Su(H)* variants, the double socket phenotype resulting from *Su(H)* overexpression prevailed (Fig. 8). Finally, consequences of *Su(H)* overexpression in the developing eye using *gmr-Gal4* were addressed (Fig. 9). As the Gal4::UAS system is temperature sensitive, phenotypes were strong at 29 °C, revealing defects in the control as well [19]. At this temperature, *Su(H)* overexpression caused overgrowth of the eye, irregular facets and necrosis. At 25 °C the phenotypes were much weaker resembling the control. A combination with *rl<sup>SEM</sup>*



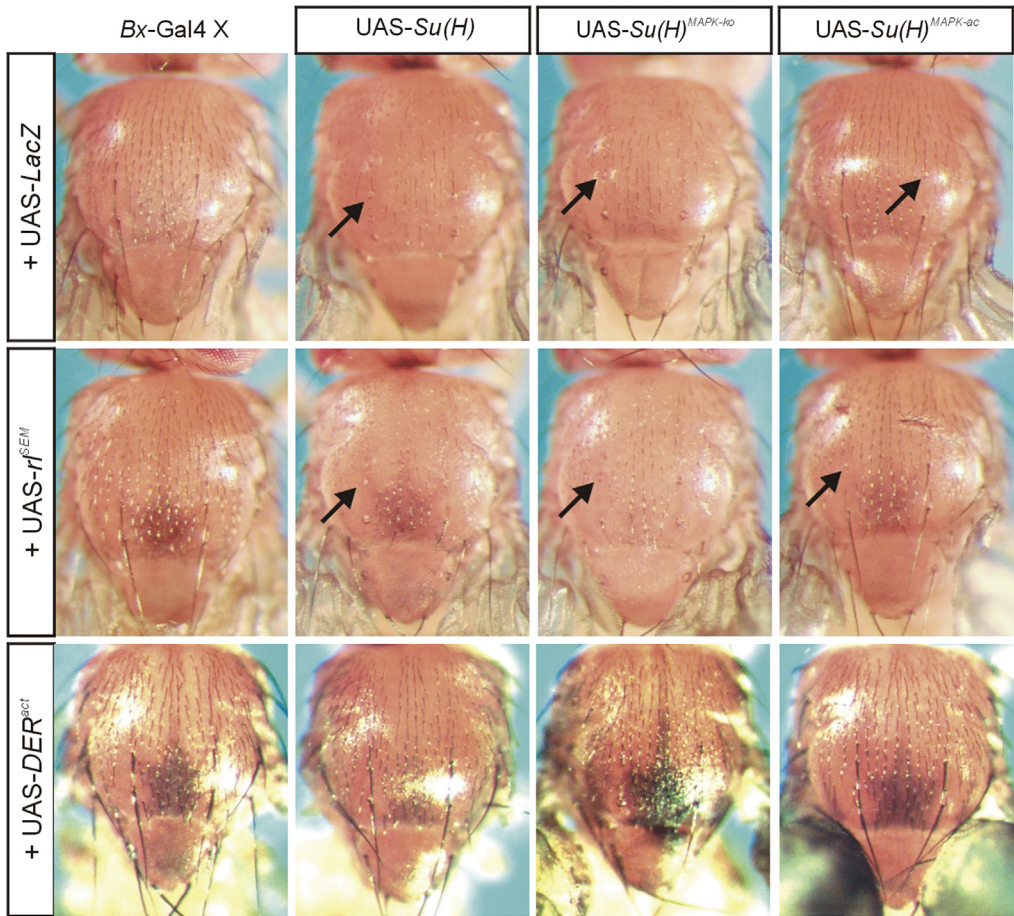
**Fig. 5.** Expression of *cut* in response to *Su(H)*, *DER<sup>act</sup>* and *r<sup>SEM</sup>* overexpression. Overexpression clones were induced in wing imaginal discs. They are labelled by the presence of GFP (green in A'–I''). Ectopic *Su(H)* protein is labelled in blue (A–I, A''–I''), and *cut* expression is shown in red (A'–I' and A''–I''). Constructs indicated at the left were under UAS-control. Note induction of *cut* upon overexpression of *Su(H)* (arrow in A'), but repression of *cut* by simultaneous overexpression of *r<sup>SEM</sup>* (C') labelled with blunt arrows. Likewise repression was seen in the combination with *Su(H)<sup>MAPK-ko</sup>* (D') but not or weakly in combination with *Su(H)<sup>MAPK-ac</sup>* (E'). *DER<sup>act</sup>* overexpression clones were frequently distorted and induced *cut* expression along the boundary to the non-overexpressing cells (arrowheads in F'–I').

enhanced the irregular facet and necrotic phenotype, whilst *gmr::r<sup>SEM</sup>* flies were very similar to the control (Fig. 9).

## 2. Experimental design, materials and methods

### 2.1. Fly stocks, husbandry and analyses

Flies were obtained from the Bloomington stock collection if not noted otherwise. Fly husbandry was according to standard protocols at 29 °C, 25 °C or 18 °C as noted. *y<sup>1</sup> w<sup>1118</sup>*, UAS-*lacZ* and UAS-*GFP* served as control. For information on fly stocks we refer to <http://flybase.bio.indiana.edu>. Adult wings of female flies were dehydrated in ethanol and mounted in Euparal (Roth, Karlsruhe, Germany) and

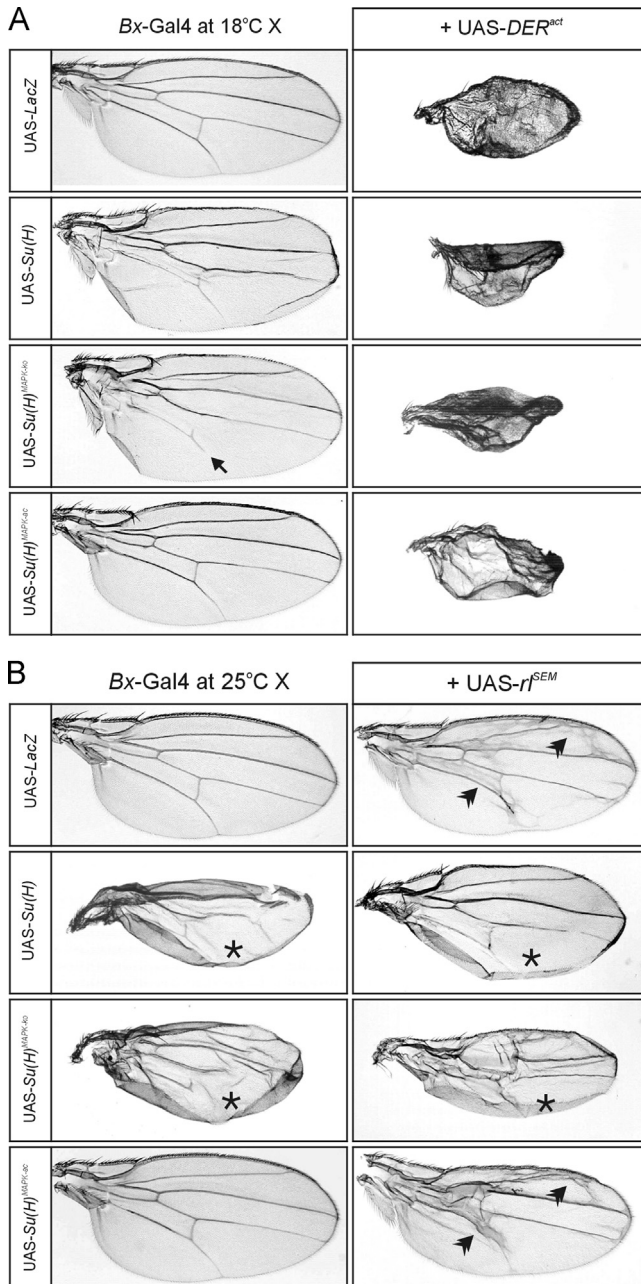


**Fig. 6.** Overexpression consequences of *Su(H)*, *DER<sup>act</sup>* and *rl<sup>SEM</sup>* during thorax development. Co-overexpression of UAS-*Su(H)* variants together with UAS-*lacZ* (control), UAS-*rl<sup>SEM</sup>* or UAS-*DER<sup>act</sup>* was driven in the developing thorax using Bx-Gal4 at 18 °C. Arrows point to examples of shaft to socket transformations that affected the majority of macrochaetae when UAS-*Su(H)* or UAS-*Su(H)<sup>MAPK-ko</sup>* were overexpressed, but were rarely observed upon UAS-*Su(H)<sup>MAPK-ac</sup>* ectopic expression. Simultaneous overexpression of UAS-*rl<sup>SEM</sup>* had little influence on each of these specific phenotypes. In contrast UAS-*DER<sup>act</sup>* phenotypes were epistatic to the overexpression of any the respective *Su(H)* constructs, i.e. all the resultant flies resembled those of the single *DER<sup>act</sup>* overexpression. Typical representatives are shown in each case.

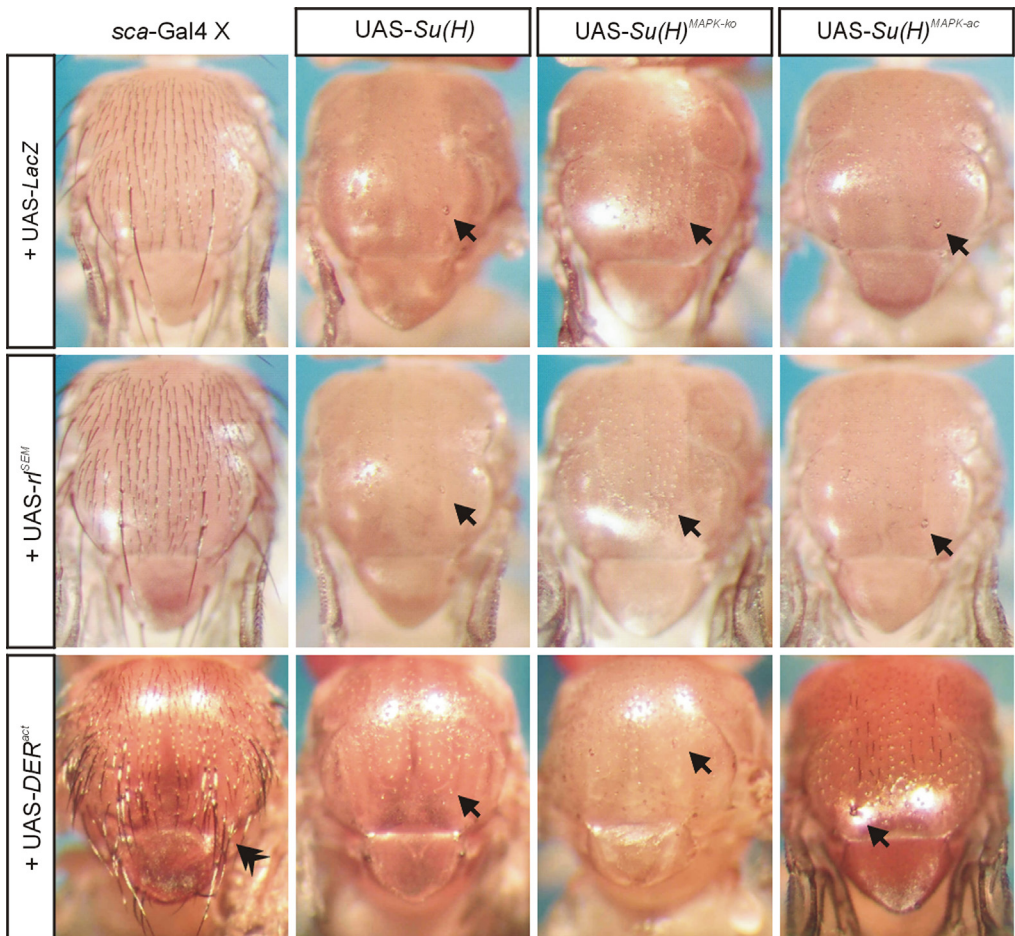
dried over night. Pictures of wings or adult flies were taken on a Zeiss Axiophot or a Wild 5M stereomicroscope, respectively, using an ES120 camera (Optronics, Goleta CA, USA) and Pixera Viewfinder software, version 2.0.

Generation of UAS-*Su(H)*, UAS-*Su(H)<sup>MAPK-ko</sup>* (T426A) and UAS-*Su(H)<sup>MAPK-ac</sup>* (T426E) was described earlier [3,20]. UAS-*rl<sup>SEM</sup>* was provided by Martín-Blanco [15] and UAS-*DER<sup>act</sup>* by Freeman [14]. LacZ-reporter gene constructs *vg<sup>BE</sup>-lacZ* and *E(spl)m8-lacZ* were kindly provided by Bray and Schweisguth [11,13]. Tissue-specific expression of respective transgenes was induced with the Gal4:: UAS-system [6] using *omb-Gal4* [7], *Bx-Gal4* [17], *sca-Gal4* [21] and *gmr-Gal4* [19]. Overexpression clones were induced by the flip-out technique [16] with the following fly lines: *y w flp<sup>1.22</sup>*; UAS-*Su(H)* or UAS-*Su(H)* mutants, *y w flp<sup>1.22</sup>*; UAS-*rl<sup>SEM</sup>* and *y w flp<sup>1.22</sup>*; UAS-*rl<sup>SEM</sup>* UAS-*Su(H)*; UAS-*DER<sup>act</sup>* and *y w flp<sup>1.22</sup>*; UAS-*DER<sup>act</sup>* UAS-*Su(H)* or UAS-*Su(H)* mutants and *y w Act > CD2 > Gal4*, UAS-*GFP-nls* (kindly provided by K. Basler).





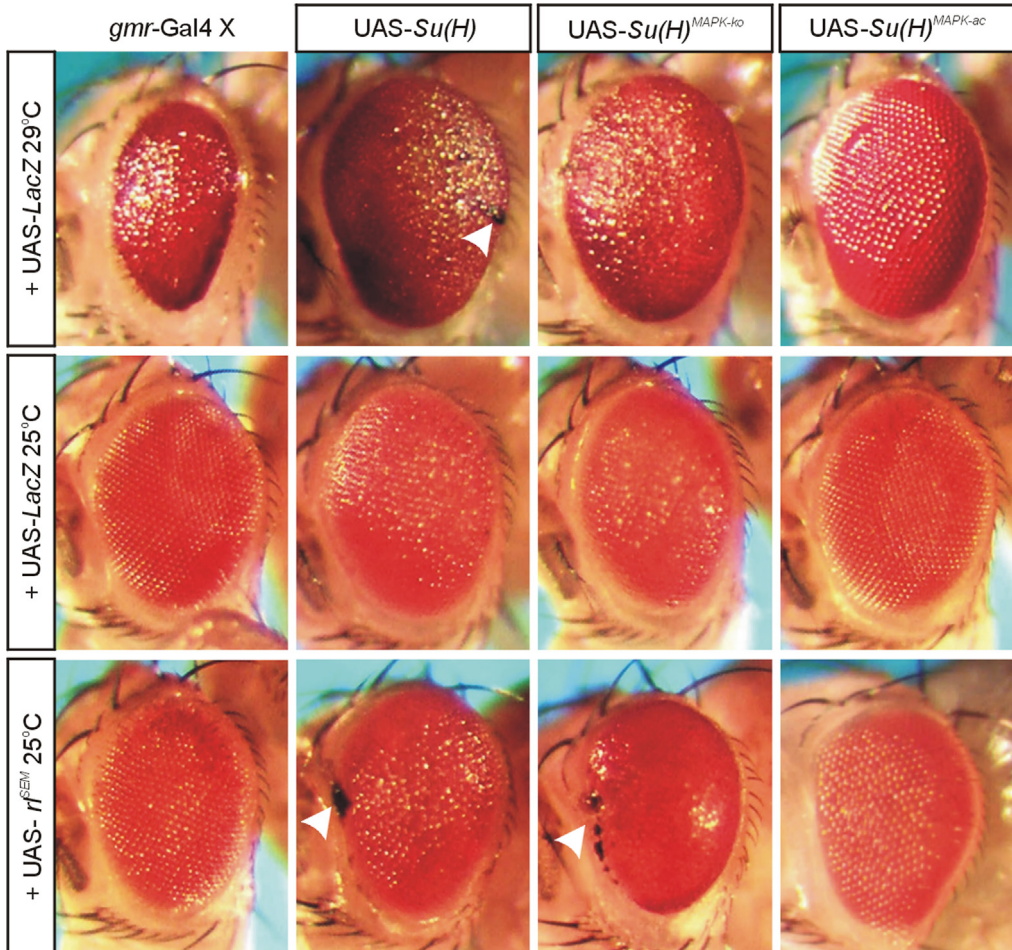
**Fig. 7.** Overexpression consequences of *Su(H)*, *DER<sup>act</sup>* and *rt<sup>SEM</sup>* during wing development. Co-overexpression of UAS-*Su(H)* variants together with UAS-*lacZ* (control), UAS-*DER<sup>act</sup>* (at 18 °C) (A) or UAS-*rt<sup>SEM</sup>* (at 25 °C) (B) was driven in the developing wing using *Bx-Gal4*. (A) At 18 °C, *Su(H)<sup>MAPK-ko</sup>* repressed vein formation (arrow) which was not observed for either *Su(H)* or *Su(H)<sup>MAPK-ac</sup>*. Induction of UAS-*DER<sup>act</sup>* resulted in very small wings mainly consisting of vein material, which was independent of *Su(H)* overexpression. As a consequence, the wings resulting from the combined overexpression were indistinguishable from those of the single *DER<sup>act</sup>* overexpression. (B) At 25 °C, overexpression of either *Su(H)* or *Su(H)<sup>MAPK-ko</sup>* but not *Su(H)<sup>MAPK-ac</sup>* induced tissue overgrowth typified by wing blisters (asterisks). Induction of UAS-*rt<sup>SEM</sup>* caused a network of veins (double arrowheads) which was repressed by the presence of ectopic *Su(H)* or *Su(H)<sup>MAPK-ko</sup>* but not by *Su(H)<sup>MAPK-ac</sup>*. At the same time *Su(H)* and *Su(H)<sup>MAPK-ko</sup>* gain of function phenotypes prevailed. Typical representatives are shown in each case.



**Fig. 8.** Overexpression consequences of *Su(H)*, *DER*<sup>act</sup> and *r*<sup>SEM</sup> in the developing bristle organs. Co-overexpression of UAS-*Su(H)* variants together with UAS-*lacZ* (control), UAS-*r*<sup>SEM</sup> or UAS-*DER*<sup>act</sup> was driven in the developing bristle organs using *sca*-Gal4 at 25 °C. Overexpression of any of the *Su(H)* variants within the developing bristle organ caused a near complete transformation of bristle shafts to sockets of micro- or macrochaetae. Examples of the resultant double sockets are highlighted by arrows. The phenotypes were nearly indistinguishable between the three *Su(H)* variants. Whereas flies overexpressing of *sca::r*<sup>SEM</sup> matched the control phenotype, *sca::DER*<sup>act</sup> developed tufts of macrochaetae on the posterior thorax (double arrowhead). Each of these phenotypes disappeared completely in a combination with any *Su(H)* variant. Typical representatives are shown in each case.

## 2.2. Immunohistochemistry

Imaginal discs were stained according to standard protocols using mouse monoclonal antibodies directed against Cut, Wingless or beta-Galactosidase (developed by G.M. Rubin, S.M. Cohen, and J.R. Sanes respectively, and obtained from DSHB or using a polyclonal antiserum directed against *Su(H)*) [22]. Secondary antibodies coupled to FITC, Cy3 or Cy5 (1:200) were obtained from Jackson Immuno-Research Laboratories (Dianova, Hamburg, Germany). Samples were mounted in Vectashield (Vector Lab) and examined on a Zeiss Axioskop coupled to a BioRad MRC1024 confocal microscope using LaserSharp 2000TM software (Carl Zeiss, Jena, Germany).



**Fig. 9.** Overexpression consequences of *Su(H)*, *DER<sup>act</sup>* and *r<sup>SEM</sup>* in the developing eye. Co-overexpression of UAS-*Su(H)* variants together with UAS-lacZ (control) or UAS-*r<sup>SEM</sup>* was driven in the developing eye using *gmr*-Gal4. At 29 °C, *gmr::lacZ* flies have smaller eyes with irregular facets giving the eye a rough appearance. In contrast, overexpression of *Su(H)* variants at this temperature causes enlarged eyes that appear slightly bulgy. Both *Su(H)* and *Su(H)*<sup>MAPK-ko</sup> induced irregularities in the arrangement of the facets and necrosis (arrowhead), in contrast to *Su(H)*<sup>MAPK-ac</sup>. At 25 °C the phenotypes are much milder, and eyes appear like wild type (*Su(H)*<sup>MAPK-ac</sup>) or slightly rough (*Su(H)*<sup>MAPK-ko</sup>). A similar rough eye phenotype was observed upon induction of *r<sup>SEM</sup>* at 25 °C. The combined overexpression of *Su(H)* and *r<sup>SEM</sup>* gave a mixed phenotype, i.e. eyes were smaller, rough and necrotic (arrowhead). Similar necrotic patches (arrowhead) and size decrease were also observed in the eyes of *gmr:: Su(H)*<sup>MAPK-ko</sup> + *r<sup>SEM</sup>* animals, which in addition had a glossy appearance. In contrast, the eyes of the *gmr:: Su(H)*<sup>MAPK-ac</sup> + *r<sup>SEM</sup>* animals looked similar to *gmr:: r<sup>SEM</sup>*. Typical representatives are shown in each case.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.dib.2015.11.004>.

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