extended β conformation of the peptide substrate would permit favorable interactions between Phe at both P3 and P1 as may occur in the rhizopuspepsin inhibitor complex.

Subsite S1 in these proteases has space for a large hydrophobic residue, which agrees with experimental observations with RSV PR showing that iodinated Tyr at P1 is cleaved more rapidly than Tyr or smaller hydrophobic residues (*8*). The Phe residue occurs at P1 in several HIV-1 cleavage sites, and there may be favorable interactions with Phe^{53}. In rhizopuspepsin, Phe may occur at P1 and P1′ due to favorable interactions with Tyr^{77} and Phe^{114} of subsite S1 and Trp^{194} and Trp^{294} in S1′. Although rhizopuspepsin binds Phe at P1′, a smaller hydrophobic side chain is predicted to fit better in subsite S1′ of the retroviral PR and Pro is often present at this location in both RSV and HIV-1 target sequences.

The substrate residue P2′ tends to be polar for HIV-1 PR and hydrophobic for RSV PR. This difference may be due to the nearby Asp^{30} in HIV-1 PR, which is replaced by a hydrophobic residue Ile^{42} in RSV PR. Further from the cleaved peptide, that is, at and beyond subsites S4 and S3′, the substrate lies near the surface of the dimer where there are several charged residues, so polar amino acids may be preferred at distal locations in the substrate. The above subsite model and other predictions from our analyses are presently being tested by site-directed mutagenesis of the PR and substrate peptides. However, these predictions provide sufficient insight into the probable features of the active site of the HIV-1 protease to be immediately useful for the design of potential inhibitors of this retroviral enzyme.

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Ubiquitous Expression of *sevenless*: Position-Dependent Specification of Cell Fate

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Specification of cell fate in the compound eye of *Drosophila* appears to be controlled entirely by cell interactions. The *sevenless* gene is required for the correct determination of one of the eight photoreceptor cells (R7) in each ommatidium. It encodes a transmembrane protein with a tyrosine kinase domain and is expressed transiently on a subpopulation of ommatidial precursor cells including the R7 precursors. It is shown here that heat shock–induced indiscriminate expression of a *sevenless* complementary DNA throughout development can correctly specify R7 cell identity without affecting the development of other cells. Furthermore, discontinuous supply of *sevenless* protein during eye development leads to the formation of mosaic eyes containing stripes of *sevenless*$^+$ and *sevenless*$^-$ ommatidia, suggesting that R7 cell fate can be specified only within a relatively short period during ommatidial assembly. These results support the hypothesis that the specification of cell fate by position depends on the interaction of a localized signal with a receptor present on many undifferentiated cells, and that the mere presence of the receptor alone is not sufficient to specify cell fate.

THE COMPOUND EYE OF *DROSOPHILA* is a suitable model system to study specification of cell fate determined by cellular interactions since the assembly of the individual ommatidia or unit eyes occurs without cell lineage restrictions (*1–3*). It has been proposed that the fate of an undetermined cell depends on its position relative to previously determined cells in the developing eye (*4*). The *sevenless* (*sev*) gene is required for the correct determination of one of the eight photoreceptor cells (R7) in each ommatidium (*5*). In the absence of a functional *sev* gene the presumptive R7 cell does not enter the proper developmental pathway and assumes a different fate (*6*). The nature of the *sev* gene product, which appears to be a receptor-type tyrosine kinase, suggests that it interacts directly with a ligand presented by a neighboring cell. This interaction would then lead to the determination of the cell through the activation of the *sev* protein (*7, 8*). Specification of cell fate by cell interactions can be viewed in at least two alternative ways. Specificity of the selection may depend on the localized presentation of a positional signal and a widespread distribution of the corresponding receptor. Conversely, selection might be dictated by the restricted distribution of the receptor interacting with a ubiquitous ligand. Although the *sev* protein is not exclusively expressed in the R7 precursor, its expression is temporally and spatially restricted within the eye disk (*9*). Therefore it

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has been proposed that the selection of R7 cell fate depends on a combination of restricted expression of both ligand and receptor (*9*).

To test whether the restricted distribution of the wild-type *sev* protein is essential for the correct specification of photoreceptor cell fate, we examined the effect of indiscriminate expression of the *sev* gene. We constructed a heat-inducible *sev* gene (*hsp-sev*) by fusing an 8.2-kb *sev* cDNA to the promoter of the *hsp70* gene (*10*). The *hsp-sev* construct was introduced into sev^{d2} null-mutant hosts by P element–mediated transformation (*11*) and four transgenic lines were obtained. Inducible expression of *sev* mRNA and protein in the transformed lines was tested by both in situ hybridization to tissue sections (*12*) and Western blots of immunoprecipitates (*13*) (Fig. 1). In contrast to the spatially and temporally restricted expression of the endogenous *sev* gene (*7, 9*) the *hsp-sev* construct could be induced ubiquitously by heat shock to produce *sev* mRNA and correctly processed *sev* protein at all stages of development.

The specification of the different cell types in the eye occurs over a period of approximately 36 hours at the end of the third larval period and the beginning of pupal development (*14*). To test whether the *hsp-sev* construct is capable of rescuing the sev^- phenotype the transformed lines were heat-shocked every 6 hours for 30 min during this period (*15*). This induction protocol resulted in the complete rescue of the mutant phenotype (Fig. 2, A and B). Thus, a *sev* cDNA driven by an exogenous heat-inducible promoter can replace wild-type gene function permitting the correct specification of R7 development.

We have not observed any apparent effect on the development of other cells caused by the ectopic expression of *sev*. In addition, the induction of *sev* every 6 hours throughout embryonic and larval development, as opposed to the third larval period only, produced no phenotypic effect other than the rescue of the mutant phenotype. Our results demonstrate that high levels of *sev* protein in embryonic and larval cells do not alter their fate. In particular, cells in the eye disk that normally do not express *sev* are unaffected by the presence of the *sev* protein. Therefore, the temporally and spatially restricted expression pattern of the endogenous *sev* gene does not appear to be important for the correct specification of R7 fate.

The *hsp-sev* lines provide a conditional *sev* gene that may be used for a direct determination of the temporal requirements of *sev* expression during R7 development. Since ommatidial assembly commences at the posterior margin of the eye imaginal disk (which will give rise to the compound eye) and reaches its anterior border after about 36 hours, the progressive stages of eye development are spatially displayed along the posterior-anterior axis of the eye. Induction of the *hsp-sev* gene every 12 hours rather than every 6 hours resulted in the formation of alternating vertical stripes of sev^+ ommatidia containing R7 cells and stripes of sev^- ommatidia lacking the R7 cells (Fig. 2C). Each stripe was about four ommatidial columns wide. This demonstrates that during the 12-hour intervals between two heat shocks the level of *sev* protein drops below a threshold such that not all R7 precursor cells can be determined correctly. These results strongly suggest that R7 cell fate can only be specified within a relatively short period during the assembly of the ommatidial clusters.

Loss of function mutations in the *sev* gene cause a cell fate transformation of the R7 cell type into a non-neuronal cell type (*6*). Ectopic expression of other homeotic genes and segmentation genes such as *Antennapedia* and *fushi tarazu* results in an altered fate of many cell types that would normally not express these genes (*16–18*). Both *Antennapedia* and *fushi tarazu* encode homeobox-containing proteins that probably act as transcriptional regulators controlling the expression of other genes, and thereby directly change the fate of the cells where they are expressed (*19*). In contrast, ectopic expression of *sev* does not produce a visible dominant phenotype. The *sev* gene encodes an integral membrane protein with a large extracellular domain and a tyrosine kinase domain on the cytoplasmic side. Therefore it is likely that R7 cell fate is controlled by the activation of the *sev* protein by an external ligand and not merely by the presence of the gene product itself as in the case of the homeobox-containing genes. The lack of a phenotypic effect of ubiquitous *sev* expression suggests that the distribution of the putative ligand for the *sev* protein is restrict-

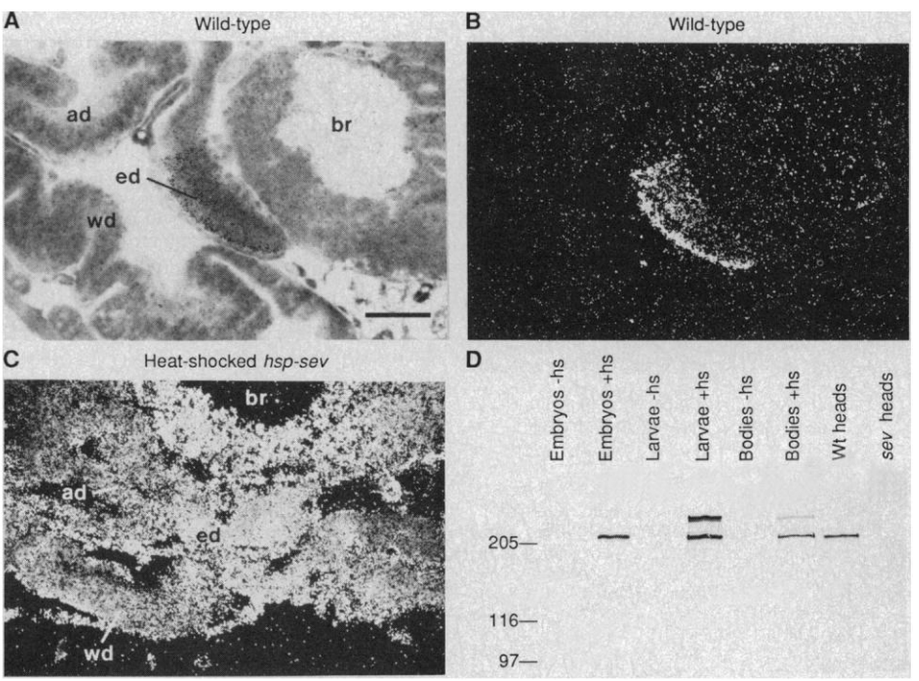

Fig. 1. Ectopic expression and inducibility of the *hsp-sev* gene. (**A**) to (**C**) show the distribution of *sev* transcripts in wild-type and heat-shocked *hsp-sev* transformants (*12*). Autoradiographs of horizontal sections through the head region of third instar larvae are shown in bright (A) and dark field (B and C). In wild-type larvae the *sev* mRNA is only expressed in a subset of cells in the eye imaginal disk (A and B). In heat-shocked *hsp-sev* larvae high levels of *sev* RNA are detected in every cell [(C), dark field of a section similar to the one shown in (A)]. No *sev* transcripts are detected in control *hsp-sev* larvae that were not heat-shocked. Abbreviations: ad, antennal imaginal disk; br, brain; ed, eye imaginal disk; wd, wing imaginal disk. Scale bar: 100 μm. (**D**) The heat-shock inducibility of the *hsp-sev* gene was assayed at different developmental stages by Western analysis of immunoprecipitates (*13*). The blot was probed with a polyclonal antiserum specific for the NH_2-terminal subunit of the *sev* protein. The 220-kD subunit is detected in wild-type heads, but is absent in heads of sev^{d2} mutants. In the *hsp-sev* transformant the 220-kD subunit of *sev* is strongly induced 3 hours after heat shock in embryos, larvae, and adult bodies. The 280-kD polypeptide that also reacts with the antiserum in the +hs lanes corresponds to the unprocessed *sev* precursor. The ectopically produced *sev* protein is indistinguishable from the endogenous *sev* protein of wild-type heads.

ed in the eye disk. A highly specific localization of the ligand for *sev* is supported by the recent analysis (*20*) of another *sev*-like locus, called *bride-of-sevenless*, which suggests that the ligand for *sev* is expressed on a single differentiating photoreceptor cell in each developing ommatidial cluster. This cell most probably corresponds to the R8 photoreceptor cell that contacts the R7 precursor.

Although it is probable that the putative ligand for *sev* is exclusively expressed in the R8 cell, even in the wild-type situation this cell is in contact with other photoreceptor cells (R3 and R4) that also express *sev*. However, R3 and R4 are not affected by the presence of the *sev* protein (*9*). In these cells the stimulation of the *sev* protein might not be sufficient to specify R7 cell fate. Alternatively, since the photoreceptor cells are integrated into the developing ommatidial cluster in a defined temporal sequence it is also conceivable that R3 and R4 have already been determined prior to the presentation of the *sev* ligand on R8. In this case specificity of R7 determination would be achieved not only by spatial but also by temporal restriction of the expression of the *sev* ligand.

Response of cells to other extracellular stimuli such as growth factors or hormones also involve specific ligand receptor interactions. However, in these cases, the signals are diffusible and hence have a widespread distribution. The cell type–restricted response to the ubiquitous signal is the result of the restricted expression of the corresponding receptor. For example, platelet-derived growth factor (PDGF) is secreted by many different tissues including blood platelets. However it stimulates only a limited set of target cells such as mesenchym-derived cells and certain glia cells (all of which contain the receptor for PDGF), but not epithelial cells or hematopoietic cells lacking the PDGF receptor (*21*). Another example is the peptide growth factor CSF-1, which stimulates growth and differentiation of certain hematopoietic precursors. Again, the specificity of the CSF-1 response is controlled by the restricted expression of the CSF-1 receptor (*22*). In contrast, the expression pattern of the receptor encoded by *sev* is not important for the position-specific determination of the R7 cell as long as it is also expressed in the R7 precursor. Our results suggest that the specificity of cell fate determination is not provided by restricted expression of the receptor but rather by a localized presentation of the signal.

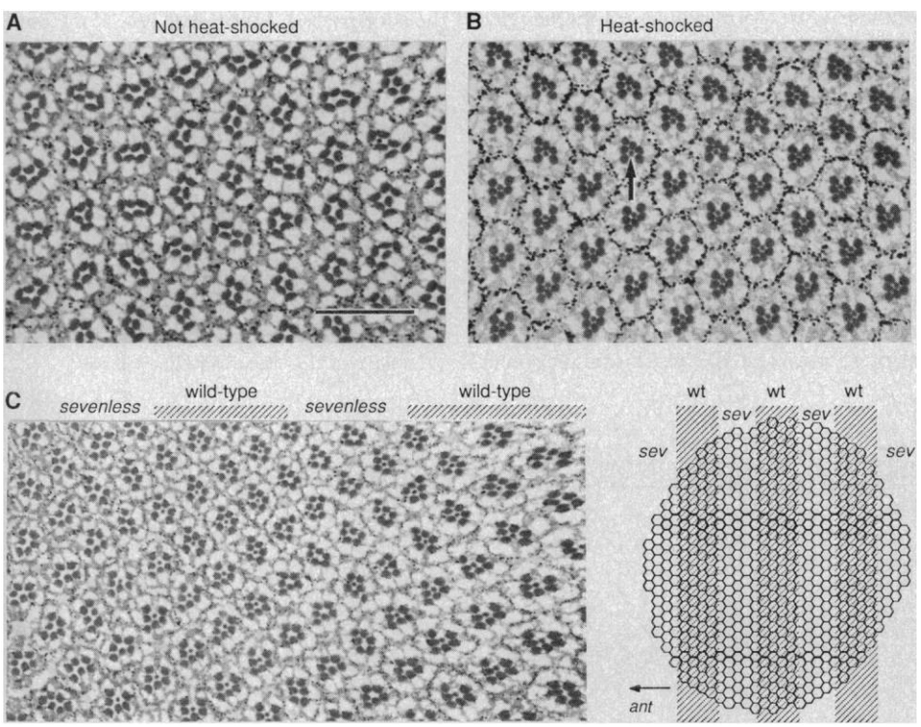

Fig. 2. Tangential sections through the eye of non–heat-shocked and heat-shocked *hsp-sev* transformants. (**A** and **B**) Repeated heat shocks every 6 hours (for 30 min at 37°C) during third instar larval and pupal development result in the complete rescue of the *sev* mutant phenotype (*15*): the centrally located rhabdomere (arrow) of the R7 photoreceptor cell is visible in every ommatidium of the heat-shocked *hsp-sev* transformant (B) but absent in the unshocked control (A). (**C**) Regional rescue of ommatidia by heat shocks applied every 12 hours instead of every 6 hours (for 30 min at 37°C) during third instar larval and pupal development. Dorso-ventral stripes of predominantly wild-type ommatidia reflect the discontinuous presence of the *sev* protein during the process of ommatidial assembly. A schematic representation of an entire fly retina illustrates the alternating distribution of sev^+ and sev^- regions in animals that have been heat-shocked every 12 hours. Scale bar: 20 μm.

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10. Construction of the *hsp-sev* fusion gene: An 8.2-kb *sev* cDNA covering all 12 exons was assembled from overlapping cDNA clones (*8*) and the last exon was fused to the corresponding 3′ genomic region to provide the endogenous termination-processing sequences. This cDNA/genomic hybrid was inserted into the P-element transformation vector pW8hsp. pW8hsp was derived from pW8 [R. Klemenz, U. Weber, W. J. Gehring, *Nucleic Acids Res.* **15**, 3947 (1987)] by insertion of a 350-bp fragment (*16*) encompassing ~250 bp of the *Drosophila hsp70* promoter and ~90 bp of the *hsp70* leader sequence [F. Karch, I. Török, A. Tissières, *J. Mol. Biol.* **148**, 219 (1981)].
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13. Western analysis: Embryos, third instar larvae, and adult flies of the *hsp-sev* transformed line ch21 were heat-shocked for 30 min (embryos) or 60 min (larvae and adults), allowed to recover for 3 hours, and then homogenized in lysis buffer. The *sev* protein was immunoprecipitated from the protein extracts with Pansorbin and goat antiserum g15-4 which was raised against a bacterial protein corresponding to amino acids 45 to 1027 of the *sev* amino acid sequence (M. Briggs, K. Basler, E. Hafen, unpublished). Equivalent amounts of protein of the unshocked controls were used in the immunoprecipitations. The equivalent of five larvae or two adult bodies was used per lane. A total of 50 heads of wild-type and sev^{d2} flies were processed for the reference lanes.
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The Human Papilloma Virus–16 E7 Oncoprotein Is Able to Bind to the Retinoblastoma Gene Product

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Deletions or mutations of the retinoblastoma gene, RB1, are common features of many tumors and tumor cell lines. Recently, the RB1 gene product, p105-RB, has been shown to form stable protein/protein complexes with the oncoproteins of two DNA tumor viruses, the adenovirus E1A proteins and the simian virus 40 (SV40) large T antigen. Neither of these viruses is thought to be associated with human cancer, but they can cause tumors in rodents. Binding between the RB anti-oncoprotein and the adenovirus or SV40 oncoprotein can be recapitulated in vitro with coimmunoprecipitation mixing assays. These assays have been used to demonstrate that the E7 oncoprotein of the human papilloma virus type–16 can form similar complexes with p105-RB. Human papilloma virus–16 is found associated with approximately 50 percent of cervical carcinomas. These results suggest that these three DNA viruses may utilize similar mechanisms in transformation and implicate RB binding as a possible step in human papilloma virus–associated carcinogenesis.

THE RETINOBLASTOMA GENE, RB1, is deleted or mutated in many human tumors or tumor cell lines, including retinoblastomas (*1, 2*), osteosarcomas (*1, 3*), small cell lung carcinomas (*4*), breast cancers (*5*), and bladder carcinomas (*6*). Inheriting a mutant allele for the RB1 gene predisposes a recipient to retinoblastoma (*7*). In all cases studied to date, the loss of the RB1 gene or the inability to synthesize p105-RB is correlated with increased cell proliferation and oncogenesis. These results have led to the hypothesis that the RB1 polypeptide plays a critical role in limiting the proliferation of certain cells. Loss of the RB protein would remove this block, thus indirectly stimulating cell proliferation.

In cells transformed or infected with adenovirus or SV40, the transforming proteins of these viruses form protein complexes with p105-RB (*8, 9*). It has been speculated that the binding of these oncoproteins to p105-RB inactivates the RB protein, thus mimicking the loss of the RB1 gene as seen in genetic predisposition to retinoblastoma. Neither SV40 nor adenovirus has been linked to human cancer (*10*). To test the possible link between the binding of p105-RB to other viral transforming proteins in the genesis of human cancer, an in vitro mixing assay (*11*) has been used to study the association of the E7 transforming protein of human papilloma virus–16 with p105-RB.

Papilloma viruses are often associated with benign, proliferative, squamous-epithelial lesions in higher vertebrates. In some cases these viruses have been associated with lesions that may progress to carcinomas. Compelling clinical and epidemiological data now link certain of the human papilloma viruses (HPVs) to a variety of human cancers, most notably cervical cancer. The most thoroughly studied of the HPVs associated with cervical carcinomas is HPV-16, the DNA of which has been found in over 50% of the cervical biopsy and tumor specimens examined (*12*). Studies with HPV-16 have revealed that the E7 gene is both sufficient and necessary for transformation of established rodent cells (*13, 14*). Furthermore, the E7 proteins from HPV-16 can cooperate with an activated *ras* oncogene to transform primary baby rat kidney cells in vitro (*14, 15*).

The transforming ability of the HPV-16 E7 protein is one of the characteristics shared with the early region 1A (E1A) proteins of adenovirus. In addition to their similar transforming abilities, E7 and E1A share transcriptional modulatory functions, in that both can stimulate transcription from the adenovirus E2 promoter (*14, 16*). Comparisons of the amino acid sequences of the E7 and E1A proteins have revealed marked similarities between the NH_2-terminus of E7 and portions of conserved regions 1 and 2 of E1A (Fig. 1) (*14, 17*). Conserved regions 1 and 2 of E1A have been shown to

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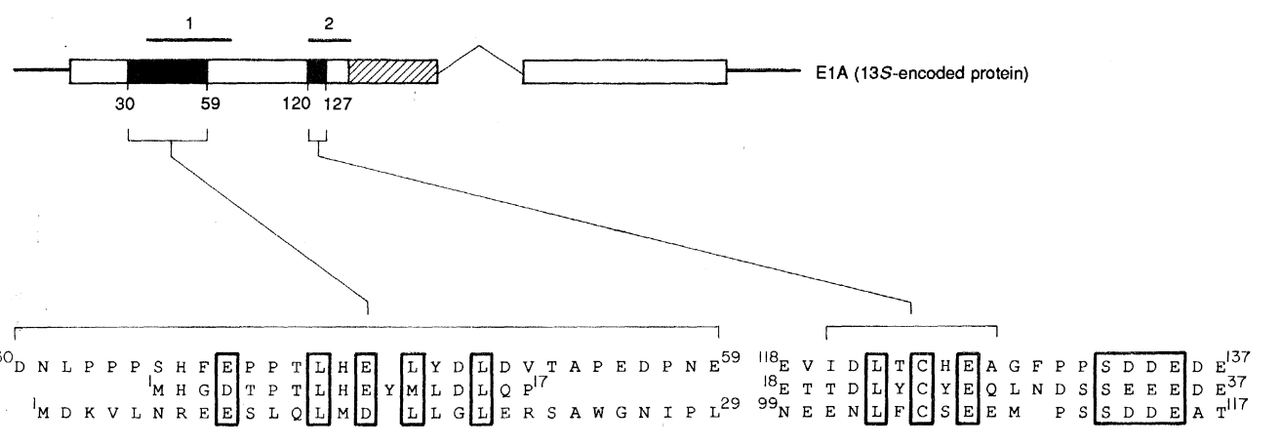

Fig. 1. Sequence homologies between the HPV-16 E7 and adenovirus E1A proteins. Regions of the E1A proteins known to be required for binding to p105-RB (*20*) are compared to homologous regions in the HPV-16 E7 proteins and the SV40 large T antigen. Only regions that are related to the p105-RB binding sites on E1A are listed. Other regions of homology are not shown [see (*14*) for further amino acid homologies]. Black boxes represent the minimal regions needed for binding of E1A to p105-RB. Corresponding regions in E7 and large T antigen are boxed if they are identical or if they represent conservative changes. Conserved regions 1 and 2 of E1A are indicated (*17*).