HEDGEHOG SIGNALLING IN DROSOPHILA AND VERTEBRATE DEVELOPMENT

by

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ABSTRACT

The hedgehog (hh) gene family encode secreted proteins that are involved in a number of developmental processes in vertebrates and invertebrates. These include the patterning of the vertebrate neural tube, somites, limb and brain and the Drosophila embryonic epidermis and larval imaginal discs. Hh proteins show a high degree of sequence identity within and between species. Recent analysis has demonstrated that this family of molecules may act in a mechanistically similar way to provide positional signalling within different phyla.

KEY WORDS: hedgehog, morphogenesis, evolution.

INTRODUCTION

The central role of non autonomous signalling factors in the morphogenesis of cell populations has long been recognised, but it is only recently that the molecular nature of these factors has been elucidated. The investigation of mutations that disrupt patterning in the embryonic cuticle and larval imaginal disc of Drosophila has defined the role of a number of secreted proteins that act at a distance to pattern fields of cells with similar developmental potentials. Strikingly, the molecular basis for such patterning seems to have been conserved between Drosophila and vertebrates, with homologues of these Drosophila genes demonstrating patterning activities coincident with signalling properties of a number of vertebrate tissues.

Perhaps the best described example of this conservation is the Drosophila segment polarity gene hedgehog (hh). The paradigm for Hh signalling was first established by the analysis of mutations in segmental patterning of the Drosophila embryo (INGHAM, 1991). Mutations which cause a loss of Hh activity are lethal and produce changes in their cuticular patterns suggestive of a requirement for the gene throughout each segment.
(Nüsslein-Volhard & Wieschaus, 1980; Mohler, 1988). This requirement contrasts with the localized expression of the hh transcript (Mohler & Vani, 1992; Lee et al., 1992; Tabata et al., 1992; Tashiro et al., 1993). Thus Hh in the dorsal ectoderm acts at a distance directly or indirectly, to pattern the epidermis. In the ventral ectoderm, however, several lines of evidence suggest instead that Hh acts at short range to control the localized expression of another signalling molecule, encoded by the segment polarity gene wingless (wg) (Ingham, 1993; Ingham & Hidalgo, 1993). As discussed below, this ability to act as both a short and a long range signalling molecule seems to have been conserved in vertebrate homologues.

The search for related genes has led to the discovery of a new family of signal-encoding genes in various vertebrate species that possess a high level of sequence identity to the Drosophila gene (Echelard et al., 1993; Krauss et al., 1993; Lee et al., 1992; Mohler & Vani, 1992; Riddle et al., 1993; Roelink et al., 1994; Tabata et al., 1992; Tashiro et al., 1993). The activity of one of these, Sonic hedgehog (Shh), in embryos of several different species presents some striking parallels with that of its invertebrate homologue.

THE HEDGEHOG GENE FAMILY

hh gene family members have been isolated from several vertebrate species including mouse (Echelard et al., 1993; Chang, 1994), chicken (Riddle et al., 1993), zebrafish (Krauss et al., 1993; Roelink et al., 1994), rat (Roelink et al., 1994), Xenopus (Ruiz I Altaba et al., 1995; Yokota et al., 1995; Ekker et al., 1995) and humans (Marigo et al., 1995). Analysis and comparison of these gene sequences reveals a number of conserved characteristics. The open reading frame of Drosophila hh encodes a polypeptide of approximately 52 kDa which is slightly larger than that of the vertebrate genes (see below, fig. 1). Hydropathy analysis has identified a highly hydrophobic region of approximately 20 residues near the N-terminus in both the vertebrate and Drosophila proteins. In vitro translation analysis suggests that this region may act either as a conventional signal

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Fig. 1. Alignment of known vertebrate Shh sequences with the Drosophila Hh protein sequence. Amino acid identities between all proteins are boxed. Cleavage sites known to occur in the Drosophila and mouse protein are indicated by arrows. The hydrophobic signal sequence is indicated by a solid line. The conserved residues with homology to serine proteases implicated in the catalysis of the internal cleavage are shaded. Amino acids conserved in vertebrates thought to generate an active site with structural homology to zinc hydrolases are indicated by asterisks, these residues are not conserved in the Drosophila protein.

(M = Mouse, R = Rat, H = Humans, C = Chicken, Z = Zebrafish, X = Xenopus.)