In the example of the a-p axis the gene products involved were inside the cell determining the position of future body parts. In the case of the dorsal-ventral (d-v) axis positional information depends on proteins outside the cell that have been secreted from a localised subset of cells. Here a secreted ligand activates target cells in a concentration depended manner through a receptor-signal transduction system. D-v axis formation in Drosophila is initiated by a signal restricted to the ventral side of the embryo, which is conveyed through the action of three extracellular serine proteases to the transmembrane receptor Toll. The earliest acting protease is Gastrulation defective (GD), followed by Snake (Snk) and finally Easter (Ea), which appears to process the Toll ligand, the cytokine like polypeptide Spaetzle (Spz) to its active form. In addition, a fourth serine protease Nudel (NdI), provided by the follicle cells during oogenesis is required to trigger the cascade. The whole proteolytic cascade is kept in check by the serine protease inhibitor Serpin27A. Through activated Spz the signal is transduced via the Toll receptor to the Cactus/Dorsal complex, which corresponds to the IkB/NF-κB complex of vertebrates. The relay of the signal is achieved through the proteins Tube and Pelle. Although Pelle is a serine/threonine kinase it does not phosphorylate Cactus directly. The Cactus kinase is presently unknown.

Cactus is phospholylated and thus targeted for degradation and the NF-κB transcription factor Dorsal is free to enter the nucleus. This regulated nuclear transport leads to the formation of a broad Dorsal gradient with highest nuclear concentrations in a narrow ventral region and rapidly declining concentrations in lateral positions. Dorsal target genes respond to different levels of the gradient and implement cell specification.
and morphogenesis across the d-v axis. For example, *snail* (*sna*) is activated by high levels of nuclear Dorsal required for mesoderm formation, while *rhomboid* (*rho*) is activated by lower levels promotes ectodermal cell fate specification (see figure below; cross sections of embryos dorsal side is facing up).

The spatially restricted activation of the protease cascade apparently depends on the modification of an as yet unknown somatically expressed heparan sulphate proteoglycan (hspg). It is presumed that the gene *pipe*, which encodes a heparan sulphate 2-O-sulphotransferase, mediates this modification. The *pipe* gene is the only one in the Toll pathway that has a ventrally restricted pattern of expression suggesting that it provides the initial spatial cues for the embryonic d-v axis. Females that lack the activity of any one of the protease genes, *spz*, *Toll*, *pipe* or *dorsal* produce dorsalised embryos, in which embryonic cells at all positions give rise to dorsal ectoderm (see figure at the bottom of the page; *wt* is a normal embryo, *pip* is an embryo lacking *pipe*; the technique used visualises the larval exoskeleton, look it up in the a-p axis handouts). Recently, the target of Pipe was found to be a protein called Vitelline Membrane-Like (VML) localised as Pipe at the anterior-lateral side of the oocyte (Zhang et al, 2009, Curr Biol 19, 1200-1205). It remains to be investigated which changes are brought about when VML is modified so that the NDL-GD-SNK-EA proteolytic cascade is activated.

As a consequence of the ventrally restricted activity of *pipe*, which leads to the proteolytic activation of SPZ there is a SPZ gradient forming with its highest pick in the ventral midline.

**Selected Reading:**
