Vulva formation in *Caenorhabditis elegans*

VULVA FORMATION IN *CAENORHABDITIS ELEGANS*

Most *Caenorhabditis elegans* are **hermaphrodites**. In their early development, they are male, and the gonad produces sperm (stored for later use) in their early development while developing the ovary as they grow old. In the nematode, the egg fertilizes when it rolls through the region where sperm are stored and then passes out of the body through an organ called the vulva.

Anchor cell formation

Anchor cells form before the development of the vulva. LIN- 12 gene in *C. elegans* is a homologue of the Notch gene, which mediates the anchor cell formation. **Z1.ppp** and **Z4.aaa are** two adjacent cells in wild-type *C. elegans* hermaphrodites and have the potential to become anchor cells. One of them becomes an anchor cell while the other becomes an interaction. Anchor cells form from **both** cells if **LIN-12** is **recessively mutated** (Loss of function mutation) however uterine precursors form from **both** cells if **LIN-12 is dominantly mutated** (Gain of function). The decision to become an anchor cell or uterine precursor cell is made in the **second** larval stage, only the uterine precursor cell needs the Lin-12 gene, and not the anchor cell is shown by **genetic mosaic** and **cell ablation** study. These two cells originally synthesize both the LAG-2 protein (homologous to Delta in Drosophila) which is a signal for uterine and the LIN-12 protein (homologous to Notch) which is the receptor for this molecule. In the particular time of larval development, one cell by chance secretes **more LAG-2**, which causes its **neighbouring cell** to **increase** the production of **LIN-12**. Gonadal anchor cells form from the cell secreting **LAG-2**. While the ventral uterine precursor cell form from the cell, which receives the signal through its **LIN-12** protein (Figure 1). Therefore, the differentiation of the two cells occurs prior to their respective differentiation event and it shows two aspects of determination are first, the initial difference between the two cells is created by chance. Second, this initial difference is reinforced by feedback. The same **LIN-12** is **activated by primary vulval** lineage to stop lateral vulval cells from forming **central vulval** phenotype during vulva formation.

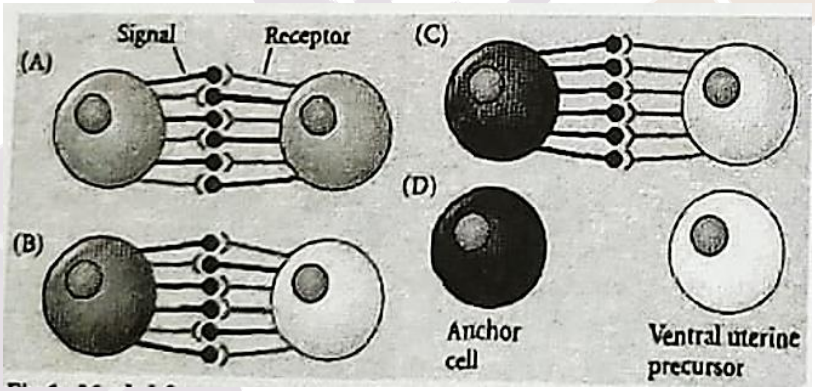

Figure 1. Model for generation of two cell types (Anchor and ventral uterine precursors) from two equivalent cells (Z1.ppp and Z4.aaa in C. elegans)

1. **Vulva formation -** One inductive signal generates a variety of cell types in the vulva formation of *Caenorhabditis elegans.* During the larval stage, vulva form from six cells called the **vulval precursor cells (VPCs).**
2. **Anchor cell** - The anchor cell is the cell, which connects the **overlying gonad** to the vulval precursor cell. The anchor cell secretes the **LIN-3** protein, which is a paracrine factor similar to mammalian epidermal growth factor (EGF) that activates the **RTK** pathway. The hypodermis (skin) is formed from VPCs instead of the vulva if anchor cells are **destroyed** or if the LIN3 gene is mutated. Six VPCs form an **equivalence group** when they are influenced by anchor cells. Each member of the equivalence group is competent to become induced by the anchor cell and depending on its proximity to the anchor cell any of three fates can be assumed (Figure 2).

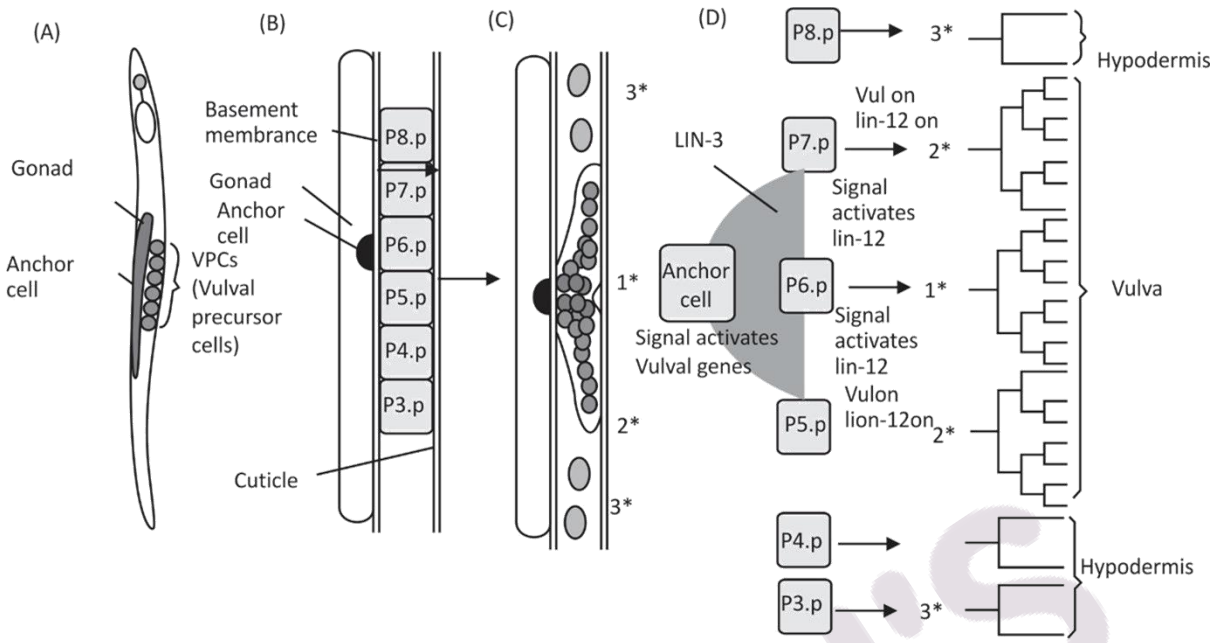

Figure 2. The *C. elegans* vulval precursor cells and their decedents

The **central** vulval cells form by the division of cells that are present directly **beneath** the anchor cell. The **lateral** vulval cells form from the division of **two cells** that **flank** the central cell, while the hypodermal cells are generated from the three cells that are **further away** from the anchor cell. The **hypodermal tissue** form from all six cells of the equivalence group if the anchor cell is **destroyed**. The vulval cells are generated from the outer three cells which normally form hypodermal cells if three central VPCs are destroyed. The VPCs have **LET-23** receptor **tyrosine kinase**, which receives the LIN-3 protein, and through the RTK pathway, the signal is transferred to the nucleus and the **LIN-31** the protein is the target of the kinase cascade. **LIN-31** protein promotes vulval cell fate by functioning as a transcription factor after its phosphorylation in the nucleus and losing its inhibitory protein partner.

Mechanisms of the Vulva formation through Induction

1. The gradient of LIN 3 protein forms and the central vulval cell is generated from the VPCs closest to the anchor cell (P6.p cell) as it receives the **highest** concentration of LIN 3 protein. Lateral vulval cells form from the two VPCS adjacent to the central cell (P5.p and P7.p) and receive a lower amount of LIN-3 protein. Hypodermis forms from the VPCs that are farther away from the anchor cells and receive not enough LIN-3 protein to show an effect.
2. After central vulval lineage is formed, two adjacent cells **(P5.p and P7.p)** are instructed to generate lateral vulval lineage by signalling through the VPCS closest to the anchor cell. This adjacent cell (P5.p and P7.p) has LIN-12 (Notch) proteins on their cell membrane, which receive the signal. The genes that specify central vulval fate are repressed and genes involved in lateral vulval fate are activated by activation of micro RNA, mir 61, by notch signal. Hypodermis forms from peripheral VPCs as they are not instructed to do anything by lateral cell

Table 1. The functions of different genes involved in vulva formation in *C. elegans*

Column A	**Column B**
Loss of functions of LIN-3	All VPCs adopt Tertiary fate
Loss of functions of LIN-3 and gain of function of LET-23	Multi – vulva
The reduced foundation of LIN-3	P6.p adopts primary fate and the rest of the VPCs adopt tertiary fate.
Overexpression of LIN-3	P.5.P, P6.p and P.7.p and adopt primary fate. P4.p and P8.p adopt secondary structures.
Gain of function of LIN-31	Multi-vulva
Loss of function of LET-23 and gain of function of LIN-3	All VPCs adopt Tertiary fate

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