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Chapter 6

Apoptosis During Cellular Pattern Formation

Masahiko Takemura and Takashi Adachi-Yamada

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1. Introduction

We can all see a variety of ordered cellular patterns consisting of various cell types, throughout nature. It is surprising that these ordered cellular patterns are created reproducibly during development in all individuals. Elucidating their underlying molecular mechanisms has been an interesting research subject for developmental biologists. The essential building blocks in these processes are cell proliferation, cell shape change, cell movement, and apoptosis. These cellular behaviors must be coordinated through cell-cell communication.

Drosophila melanogaster has provided many insights into the underlying mechanisms of many biological processes, including tissue patterning. One typical example is the ordered pattern of bristles which cover the whole body of the adult fly. In these bristles, the thorax and wing margin ones (Figure 1A, 1C, and 1D) have been examined extensively for this purpose. Specification and development of these bristles have been well studied [1]. When a single sensory organ precursor (SOP) is specified in an epithelial field, the SOP prevents its neighboring cells from choosing the same cell fate by activating Notch signaling there. This Notch-mediated lateral inhibition ensures the proper number and spatial separation of SOPs. The SOP then undergoes a series of asymmetric cell divisions, producing the components of sensory bristles, such as a shaft, socket, sheath, glial cell and neuron. However, whether the lateral inhibition is sufficient to create the final intricate pattern of bristle distribution is unknown.

Apoptosis is used extensively to refine developing structures, such as in formation of vertebrate digits and sculpting of the insect wing [2]. Apoptosis also contributes to tissue patterning by removing abnormal cells [3-5] and eliminating excess populations of cells [6].

Difference in adhesiveness between cell types is another important factor in tissue patterning. Differential adhesion mediated by heterophilic adhesion molecules forces cells to rearrange during development. For example, in the oviduct epithelium of the Japanese

quail, two distinct types of columnar cells; goblet-type gland cells and ciliated cells are arranged in a checkerboard pattern (Figure 1E) [7]. Preferential adhesion between different cell types rather than between cells of the same type could account for this pattern [8].

Experiments have shown that spatial and temporal regulation of apoptosis or cell adhesion is indispensable for correct patterning. Inappropriate cells must be removed at the proper time by apoptosis and each living cell must attach properly to its counterparts. How are these processes regulated? In this chapter, we will describe the *Drosophila* eye and posterior wing margin, which are interesting tissues showing geometrically ordered repetitive cellular arrangements (Figure 1B, 1C, and 1D). We first describe their unique cellular arrangement and then follow the patterning process. We will also explain the underlying mechanisms, which seem to be conserved in both tissues. Furthermore, we will end with a discussion of the cellular patterning of the mammalian organ of Corti.

2. *Drosophila* eye patterning

A striking example of ordered cellular packing is the *Drosophila* compound eye. It is comprised of approximately 750–800 ommatidia, which are arranged in a hexagonal close packing manner. Each ommatidium contains eight photoreceptors, four cone cells, and two primary pigment cells. At the early stage, each ommatidium is surrounded by a few layers of the interommatidial precursor cells (IPCs). These cells undergo dynamic cell rearrangement and eventually differentiate into the secondary and tertiary pigment cells which optically insulate ommatidia, and the mechanosensory bristles (Figure 2). Apoptosis plays an important role in this cell rearrangement [10]. Approximately one-third of IPCs are eliminated through apoptosis between 24 and 40 hours after puparium formation (APF) [11, 12]. As a result of apoptosis, only a single layer of IPCs surrounds each ommatidium.

The remaining two-thirds of the interommatidial cells, which are in contact with ommatidia, do not undergo apoptosis. Spatial regulation of apoptosis is mediated by epidermal growth factor receptor (EGFR) signaling [13]. Spitz, a ligand of EGFR, is produced in the primary pigment cells and secreted around surrounding cells. This activation of EGFR signaling downregulates the activity of Hid, a proapoptotic protein, which prevents these adjacent cells from undergoing apoptosis [14, 15]. In this fashion, only non-adjacent IPCs lack the EGFR signal and thus undergo apoptosis.

3. *Drosophila* wing margin hairs

The *Drosophila* posterior wing margin hair is another interesting example of ordered arrangement of cells. They are aligned along the posterior wing margin with two rows in a zigzag manner. Recently, we elucidated the patterning process of the posterior wing margin hairs [16]. Since thsese wing margin hairs are comprised of only shaft and socket cells [17], they do not work as sensors; rather they may affect airflow over the surface of the wing or protect the wing margin. We call both shaft and socket cells “hair cells” here. The zigzag alignment patterning of the hairs also requires apoptosis-related cell rearrangement as seen in the eye patterning described above. At an early stage of pupal development (20 hours

APF), hair cells are not positioned in a zigzag manner, but rather at random. However, the rearrangement of wing margin cells occurs and, by 30 hours APF, the zigzag pattern is created (Figure 3). After apoptosis, wing margin cells can be classified into two distinct types: one is 'interhair cell' which is aligned in the same row of hair cells alternatively, and 'tooth cell' which is located on the dorsoventral boundary side of hair cells and named after the teeth of a zipper. The zigzag pattern of hair cells is ensured by interlocking arrangement of these two kinds of cells. As a result of the cell rearrangement, the dorsal and ventral edges interlock.

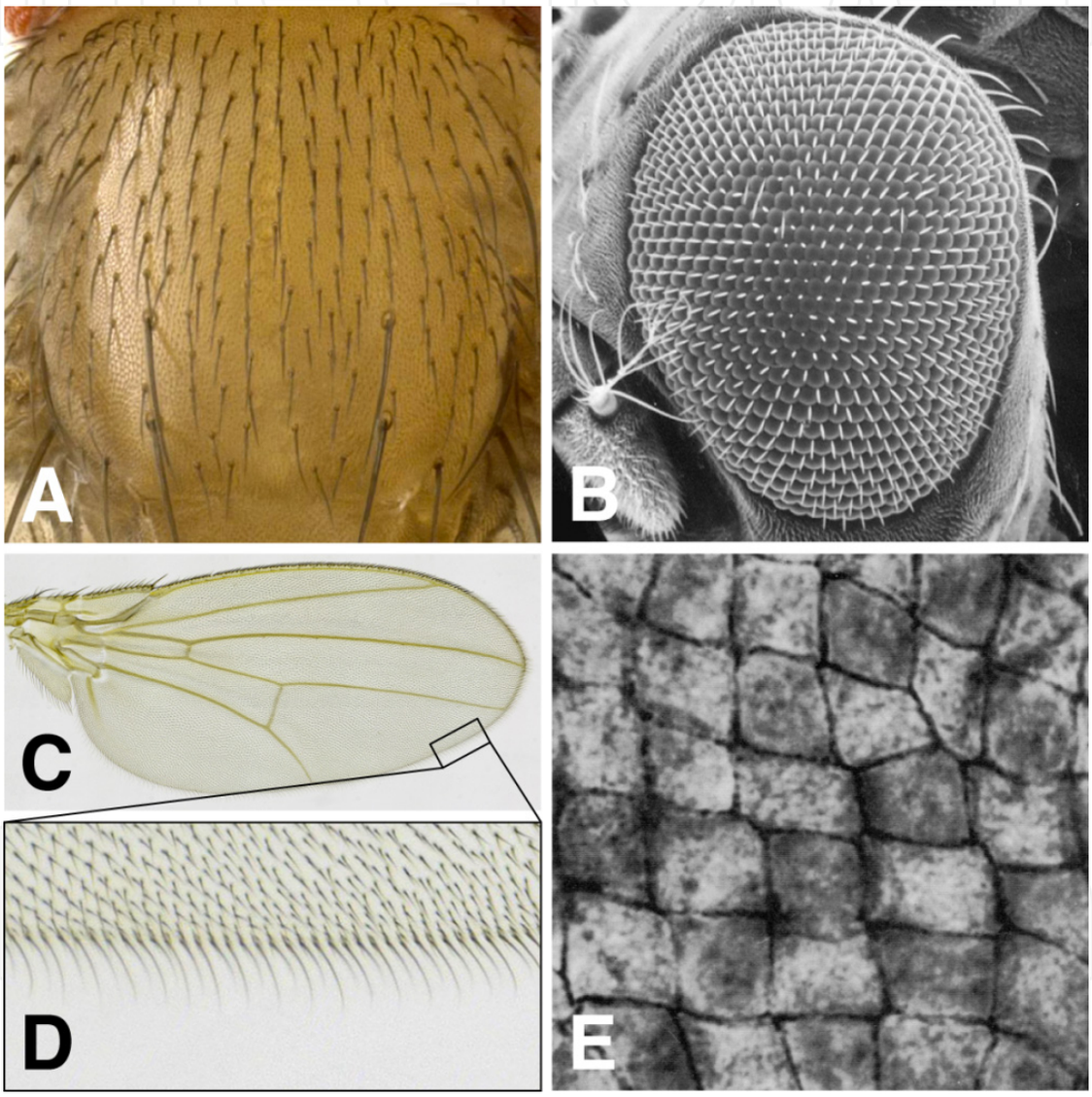

Figure 1. Elaborate biological patterns. (**A**) Macrochaetae (thick and long bristles) and microchaetae (thin and short bristles) on the *Drosophila* adult notum shows a stereotypical pattern. (**B**) SEM image of the *Drosophila* compound eye, which is comprised of 750–800 ommatidia arranged in a precise honeycomb-like pattern. Mechanosensory bristles are found at alternate vertices of the hexagonal array. (**C**) *Drosophila* adult wing. (**D**) Higher magnification view of the posterior wing margin (the boxed region in C). Wing margin hairs are aligned in even intervals. (**E**) Oviduct epithelium of the Japanese quail shows a checkerboard pattern, comprised of goblet-type gland cells and ciliated cells. This image is adapted from Honda *et al.* [9].

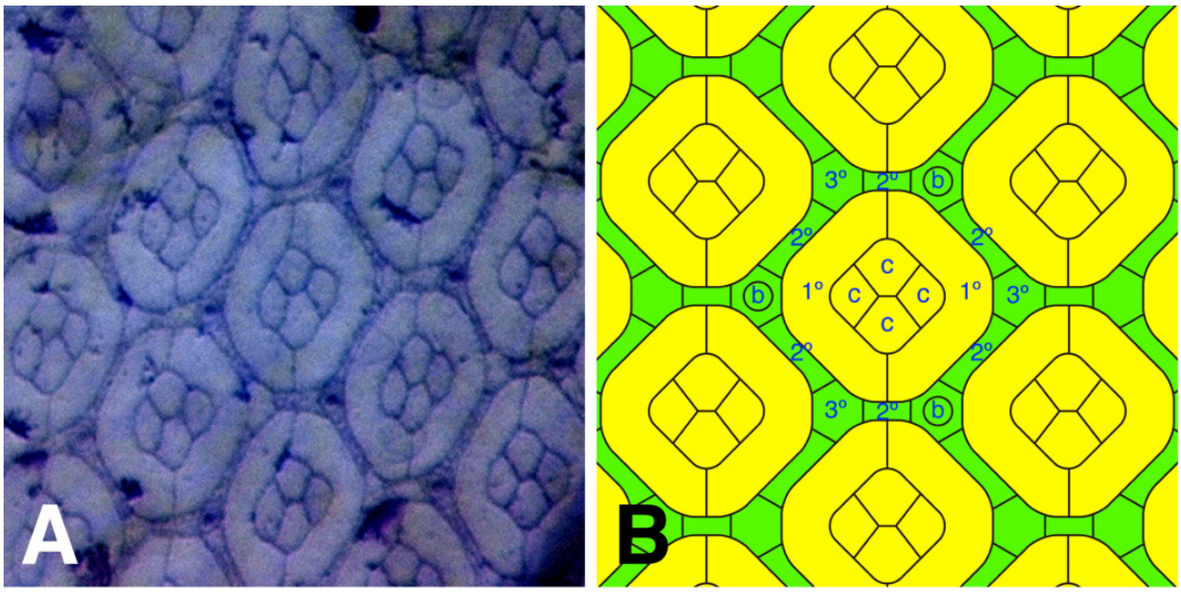

Figure 2. *Drosophila* pupal retina. (**A**) Cobalt sulfide staining of pupal eye. The photoreceptor cells are out of focus in this picture. (**B**) Schematic drawing of pupal eye. Each ommatidium is surrounded by the secondary and tertiary pigment cells, and bristles. Abbreviations: c, cone cell; 1°, primary pigment cell; 2°, secondary pigment cell; 3°, tertiary pigment cell; b, bristle.

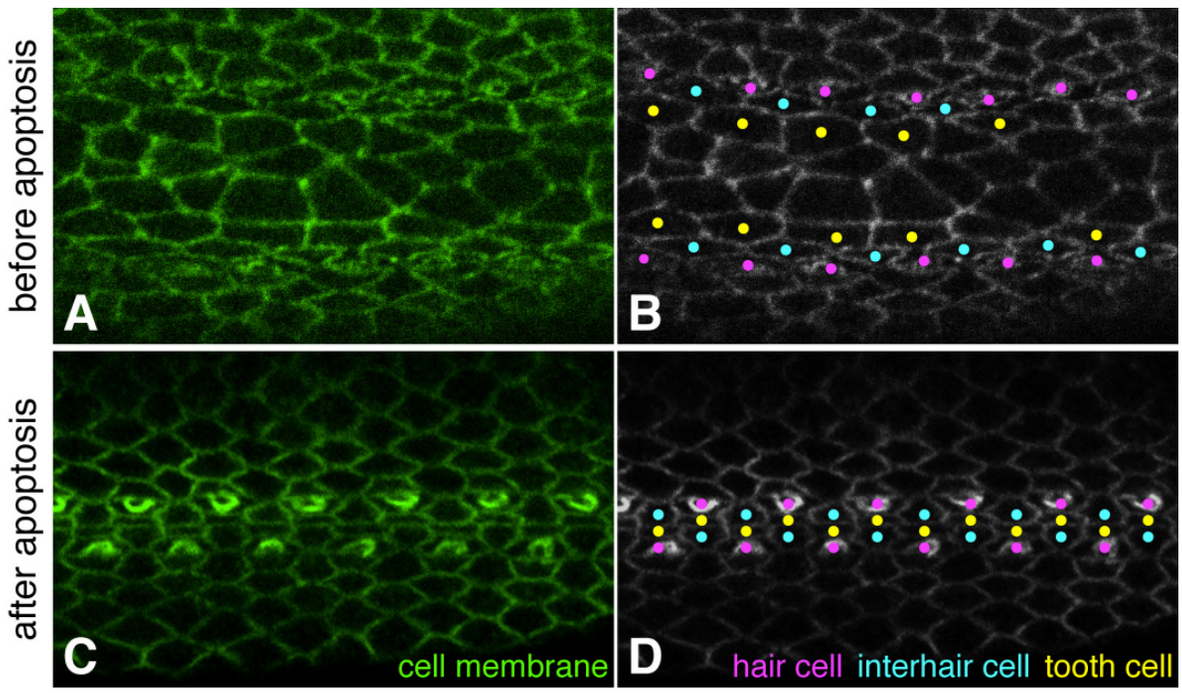

Figure 3. Zigzag pattern formation of wing margin hairs. Cellular arrangement of the *Drosophila* posterior wing margin before (A, B: 20 hours APF) and after (C, D: 30 hours APF) rearrangement. Cell membrane is marked by E-cadherin expression (green in A, C; white in B, D). Hair cells (shaft and socket), interhair cells, and tooth cells are marked by magenta, cyan, and yellow circles, respectively (B, D). (**A**, **B**) Before apoptosis, posterior wing margin cells are not arranged in an ordered manner. At this stage, hair cells are not positioned in a zigzag manner. (**C**, **D**) After cell rearrangement, hair cells, interhair cells, and tooth cells establish their unique cell shapes and are aligned in a surprisingly ordered manner. Note that the double row of hair cells is aligned in a zigzag manner.

During this cell rearrangement, a subset of wing margin cells is removed through apoptosis. The dying cells are the cells that have not attached to the hair cells. Blocking apoptosis by expressing the baculovirus caspase inhibitor p35 [18] in wing margin cells using the GAL4/UAS system [19] inhibits cell rearrangement, indicating that apoptosis is required for this process.

What triggers apoptosis in a precise temporal manner? Ecdysone, an insect steroid hormone, is indispensable for progression in most of the developmental stages of *Drosophila*. In addition, ecdysone triggers several apoptotic events associated with metamorphosis through binding with ecdysone receptors and induces expression of proapoptotic genes, such as *hid* and *reaper* [20]. During insect metamorphosis, many larval tissues, including the salivary gland and midgut, are eliminated through apoptosis. Blocking ecdysone signaling by expressing a dominant-negative form of the ecdysone receptor in wing margin cells results in excess wing margin cells, indicating that apoptosis is blocked. Thus, ecdysone signaling is required for inducing apoptosis in wing margin cells as well as in other tissues during metamorphosis.

Then, how is apoptosis in the developing tissue regulated in a precise spatial manner? Vein, a diffusible ligand of EGFR, is expressed specifically in the hair cells. In addition, EGFR activation is observed in cells surrounding hair cells, as revealed by the expression of *sprouty*, which is a target gene of EGFR signaling in the wing. These results indicate that EGFR signaling is activated in a paracrine manner in the posterior wing margin and that its activation pattern correlates with the cell survival pattern there. To confirm the relationship between the activation of EGFR signaling and cell survival of wing margin cells, we used the TARGET system, which combines the GAL4/UAS system [19] and a temperature-sensitive version of GAL80, a GAL4 inhibitor [21]. This system allows us to induce transgene expression in a desired spatiotemporal manner. Activation of EGFR signaling by expressing Ras^{V12}, a constitutively active form of its downstream activator Ras [22], in the wing margin during 0~30 hours APF, results in excess wing margin cells. On the other hand, knockdown of EGFR by expressing an inverted repeat complementary to *Egfr* mRNA (for RNAi) or a dominant negative form of EGFR results in ectopic apoptosis. Both of these genetic manipulations result in disruption of the zigzag pattern. Taken together, we found that the hair cell produces the signaling ligand molecule Vein for cell survival, which allows the surrounding cells that receive the ligands to survive.

4. Coordination of preferential adhesion and secreted survival signaling molecules

In both tissues described above, locally diffusible ligands are used to make neighboring cells survive. Thus, regulation of cell-cell contact is an important factor for controlling the spatial pattern of apoptosis. In both cases, *Drosophila* NEPH1/Nephrin homologs, which are transmembrane proteins belonging to the immunoglobulin superfamily, are involved in the preferential adhesion between cell types. In humans, mutations in the nephrin gene are associated with the congenital nephrotic syndrome of the Finnish type [23]. The

NEPH1/Nephrin homologs can be classified into two subfamilies, NEPH1 and Nephrin, that regulate many biological processes through heterophilic cell adhesion between NEPH1 and Nephrin groups, including myoblast fusion [24, 25], axonal pathfinding in the visual system [26-28], retinotopic map formation [29]. The NEPH1/Nephrin homologs are also involved in the formation of a slit diaphragm-like structure in the *Drosophila* nephrocyte, an analog of the mammalian podocyte in the kidney [30, 31]. In *Drosophila*, there are four members of the NEPH1/Nephrin subfamilies: two members of the NEPH1 subfamily, *kin of irreC* (*kirre*, also known as *dumbfounded*) and *roughest* (*rst*), and two members of the Nephrin subfamily, *hibris* (*hbs*) and *sticks-and-stones* (*sns*) [32-34, 27, 35, 36].

In the compound eye, immunohistochemical staining reveals that all four molecules accumulate at the interface between ommatidia and IPCs [37, 38]. Hibris and Sns are expressed in the ommatidia, and their binding partners Kirre and Rst are expressed in the IPCs. Computer simulation have shown that preferential adhesion between ommatidia and IPCs contribute to the cell rearrangement [10].

Similarly, antibody staining of the pupal wing indicate that all these adhesion molecules accumulate the interface between hair cell and their neighboring cells [16]. Enhancer-trap reporters for these genes also show that NEPH1 groups and Nephrin homologs are expressed in an almost complementary pattern (Figure 4). Cell-type-specific knockdown of these molecules results in disruption of the wing margin pattern. For instance, when we knockdown Rst in interhair cells, we observed some hair cells away from interhair cells and tooth cells (unpublished data). Knockdown of each gene results in disruption of the posterior wing margin hairs, indicating that all four of these molecules are required for proper hair patterning.

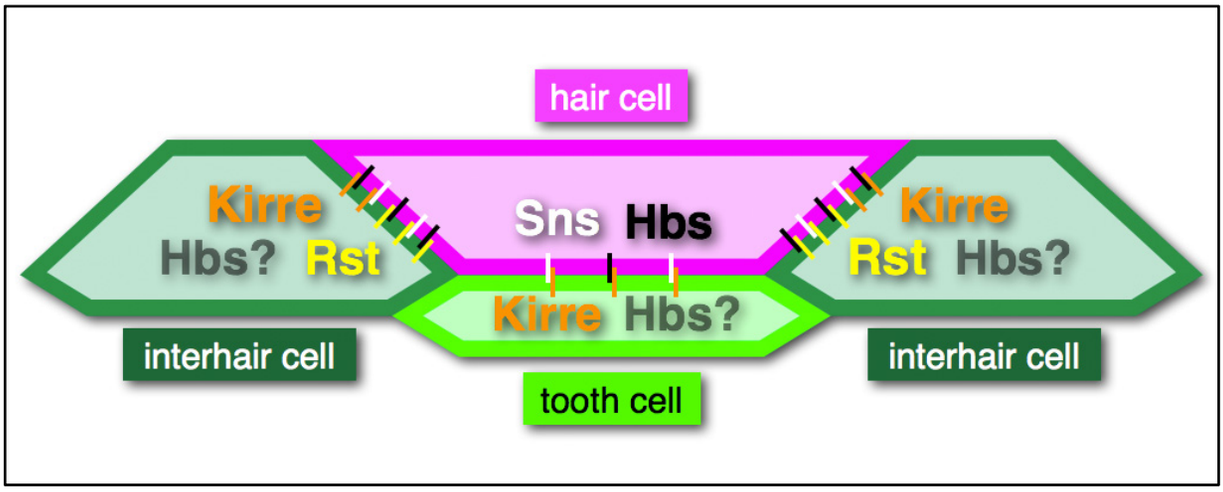

Figure 4. Expression pattern of NEPH1/Nephrin homologs in the *Drosophila* posterior wing margin. Schematic drawing of the allocation of hair cell and the neighboring wing margin cells (interhair/tooth cells). Nephrin homologs (Sns and Hbs) are expressed in the hair cell and NEPH1 homologs (Kirre and Rst) are expressed in the interhair cell and tooth cell. These molecules accumulate at the interface between hair cells and interhair cells or tooth cells. This complementary expression pattern of these heterophilic adhesion molecules contributes to the attachment between hair cells and interhair/tooth cells.

Therefore, in both the *Drosophila* eye and posterior wing margin, apoptosis-dependent cell rearrangement is strictly regulated by secretion of EGFs and preferential adhesion between cell types through heterophilic adhesion molecules.

This seems to be a good strategy for creating ordered repetitive cellular patterns through refinement (Figure 5). It is tempting to speculate that similar mechanisms work in other tissues of other organisms. Lastly, we will discuss the cellular patterning in the cochlea, a mammalian inner ear organ.

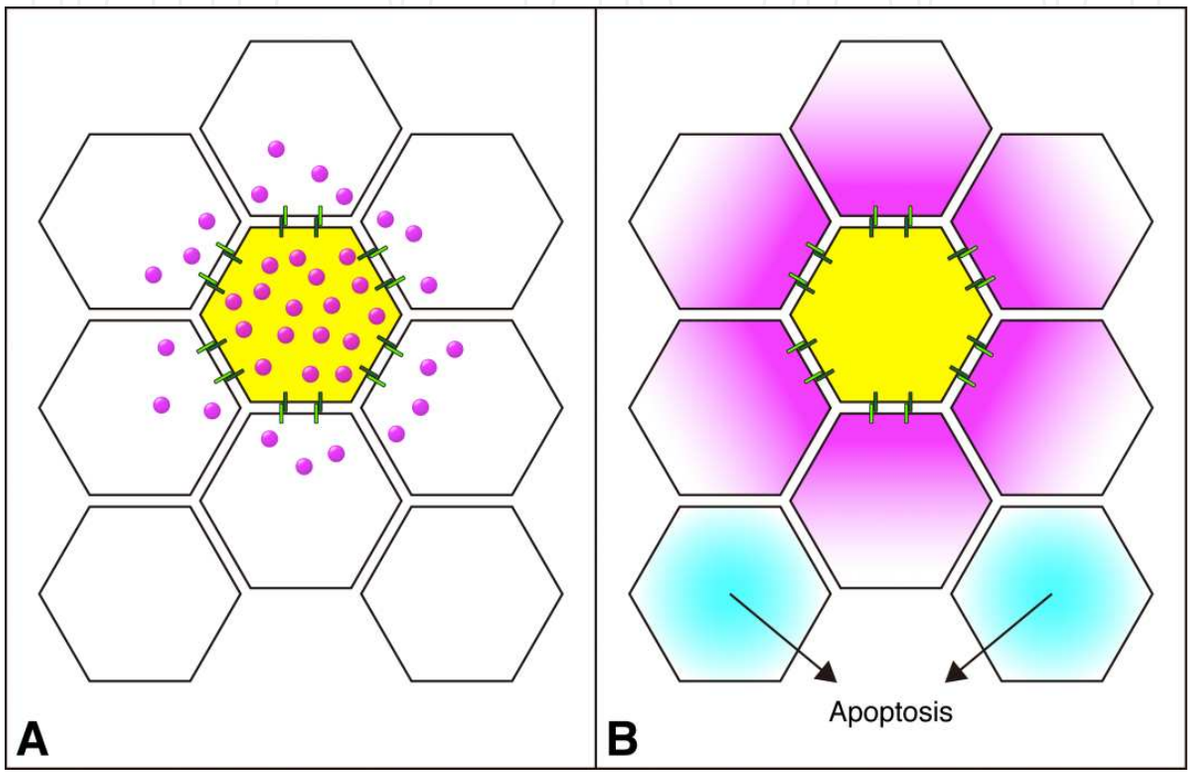

Figure 5. Model for cooperation between preferential cell adhesion and locally-secreting cell survival signal. (A) Locally-diffusing signaling molecules (magenta circles) secreted by a cell (yellow). Heterophilic adhesion molecules (light or dark green bars) attach the cell to its neighboring cells. (B) Locally-diffusing signaling molecules required for cell survival allow cells that neighbor the signaling center to survive. Cells that do not receive enough cell survival signaling molecules are destined to undergo apoptosis (cyan cells).

5. Patterning of outer hair cells and supporting cells in the organ of Corti

The sensory epithelium of the mammalian cochlea, the organ of Corti, has three rows of outer hair cells and supporting cells, which are aligned in a checkerboard pattern (Figure 6). Outer hair cells (OHCs) are essential for the amplification of sound [39] and the loss of these cells can lead to hearing loss. Specification of hair cells and supporting cells are mediated by Notch-mediated lateral inhibition [40-42], as is the case with *Drosophila* bristles. Recently, another adhesion molecules of the immunoglobulin superfamily, nectins, were found to be involved in patterning of the inner ear [43]. Mammals have four distinct nectins that mediate both homophilic adhesion and heterophilic adhesion with nonidentical nectins.

Heterophilic adhesion is stronger than homophilic adhesion. Nectin-1 is expressed in outer hair cells, nectin-3 in supporting cells, and nectin-2 in both. In the nectin-1 or nectin-3 KO mice, disruption of the checkerboard pattern is observed. Although the contribution of apoptosis for this cellular pattern remains unknown, it is a reasonable hypothesis that apoptosis may contribute to removal of excess OHCs and supporting cells. Thus, similar refining mechanisms of cellular arrangement as describe above may be conserved across species in a wide variety of multicellular organisms.

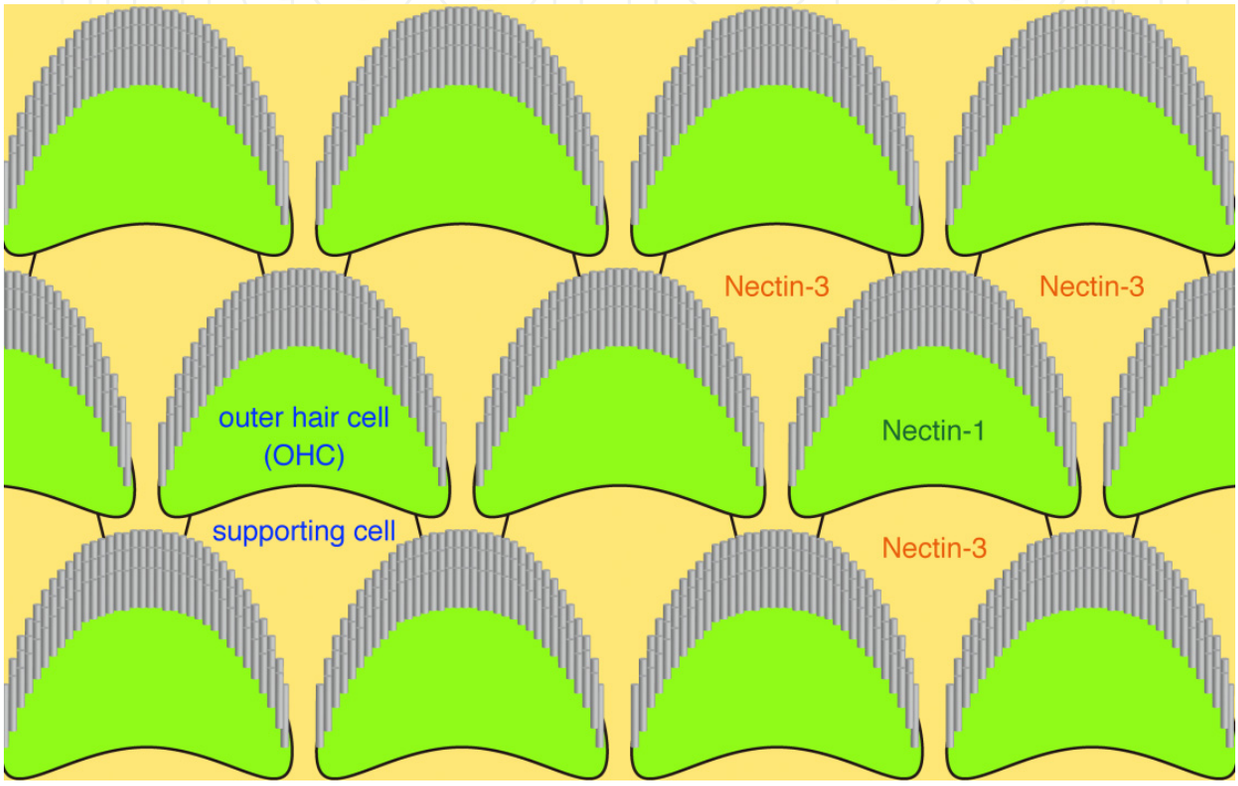

Figure 6. Schematic drawing of the arrangement of OHCs and supporting cells in the organ of Corti. Three rows of OHCs and supporting cells are arranged in an alternatively distributed pattern. This pattern can be formed by heterophilic adhesion between Nectini-1 and Nectin-3, which are expressed in OHC and supporting cell, respectively.

6. Conclusion

We have described the apoptosis-dependent cell rearrangement for refining cellular arrangements of the *Drosophila* eye and posterior wing margin. In both tissues, secreted extracellular signaling molecules to promote cell survival and heterophilic adhesion molecules are involved in correct attachment between the various cell types, which are essential for patterning. This strategy seems to reasonably achieve the geometrically ordered packing of cells and may be a conserved method in other tissues of other organisms, such as the mammalian organ of Corti.

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