Cellular recognition and patterning in sensory systems

Togashi, Hideru

Katsunuma, Sayaka

(Citation)
Experimental Cell Research,358(1):52-57

(Issue Date)
2017-09-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90005188

Cellular Recognition and Patterning in Sensory Systems

Hideru Togashi [1,*] and Sayaka Katsunuma [1, 2, 3]

[1]Division of Molecular and Cellular Biology, Department of Biochemistry and Molecular Biology,

[2]Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan

[3]Hyogo Prefectural Kobe Children's Hospital, Kobe 650-0047, Japan

***Correspondence:**

Dr. Hideru Togashi

htogashi@med.kobe-u.ac.jp

Abstract

Cells dissociated from various tissues of vertebrate embryos preferentially reaggregate with cells from the same tissue when they are mixed together. This tissue-specific recognition process in vertebrates is mainly mediated by a family of cell adhesion molecules because of their specific binding properties. Recent studies have revealed that two families of adhesion molecules, nectins and cadherins, are associated with each other, and these associations provide cells with the differential adhesive affinities required for cellular recognition and complex cellular pattern formations during development. This review provides an overview of recent findings regarding the cooperative functions of nectins and cadherins, as well as a discussion of the molecular basis underlying these functions.

Keywords: cell recognition, cell sorting, mosaic cellular pattern, cadherins, nectins, hippocampal neurons, sensory organs

Introduction

Cells dissociated from various tissues of vertebrate embryos preferentially reaggregate with cells from the same tissue when they are mixed together. This tissue-specific recognition process in vertebrates is mediated by various cell adhesion molecules that hold cells together by homophilic or heterophilic interactions between such transmembrane proteins on adjacent cells. Some cell–cell junctions are asymmetric or heterogeneous. For example, synapses are asymmetric junctions that are usually formed between axons and dendrites, myelin is formed between neurons and supporting glial cells, and the sensory epithelium consists of heterogeneous junctions between sensory and supporting cells. These asymmetric or heterogeneous junctions are generally found in a variety of tissues and organs. Selective cell–cell adhesion between different cell types is fundamental for cell recognition and sorting different cell types in morphogenesis. Recent advances have clarified the molecular compositions of various cell interfaces and provided new insights into asymmetric or heterogeneous cell–cell recognition and junction formation. Cell–cell junctions contain various transmembrane proteins, cytoskeletal elements, and signaling complexes. A single cell type employs multiple molecular mechanisms for adherence to other cells. The specificity of cell–cell adhesion in development results from the integration of several adhesion systems. Here,

we briefly review the cooperative roles of nectins and cadherins in cell recognition and adhesion during asymmetric or heterogeneous cell–cell junction formations. These mechanisms also explain the organization of highly ordered cellular patterns in complex sensory organs.

Molecular basis of cadherins and nectins in cellular recognition and adhesion

Cadherins are adhesion molecules involved in adhesion and selective cell–cell recognition of vital biological processes such as embryogenesis, pattern formation, and neural circuit formation [1]. Cadherins constitute a superfamily and are grouped into subfamilies designated as classic cadherins and proto-cadherins. The defining feature of classic cadherins is the presence of a conserved intracellular domain that mediates cytoplasmic interactions with catenins. Here, for convenience, classic cadherins are simply referred to as cadherins. Cadherin molecules associate with p120 catenin and β-catenin via their cytoplasmic domain, and β-catenin in turn binds to α-catenin. α-Catenin interacts with F-actin, and an interaction between the cadherin-catenin complex and actin cytoskeleton is thought to be crucial for cadherins to create firm cell adhesions **(Fig.1A)** [2]. The expression patterns of multiple cadherins and their dynamic changes during development are the most fascinating features observed in the cadherin family. In mixed

cultures of cell lines expressing different types of cadherins, the cells form separate aggregates according to their homophilic binding property **(Fig.1B)** [3]. Through their selective adhesive property, cadherins are thought to be the main driver of various morphogenetic events [4, 5]. Binding specificity of cadherins is attributed to the extracellular domain because exchange of this domain between two different cadherins determines cell aggregation and sorting specificity [6, 7]. Many subtypes of cadherins are expressed by restricted groups of cells in tissue and their expression patterns correlate with tissue organization. The expression pattern of each cadherin subclass in embryos correlates with the positional segregation of cell populations. However, there are only a few examples of cadherin-dependent tissue segregation, such as positioning of oocytes during ovary development in the fly, boundary formation between the cerebral cortex and striatum in the mouse brain, and segregation of motor neurons in the chick spinal cord [8]. Cadherins also contribute to cell segregation by differential expression levels of a single cadherin type. Cells expressing high levels of cadherin sort out from cells expressing low levels of the same cadherin in vitro [9]. During gastrulation in vertebrate development, different progenitor cells expressing the same cadherin type sort out and assemble into distinct germ layers. These processes occur by graded variations in cadherin density, and localized expression of adhesion-modulating factors are associated

with regional differences in adhesive properties. In particular, differential actomyosin-dependent cell–cortex tension is important to direct progenitor cell sorting [10]. Molecular mechanisms that underlie cadherin-catenin complexes and actomyosin interactions remain to be analyzed further.

Nectins, which were originally identified as virus receptors, are Ca^{2+}-independent immunoglobulin (Ig)-like cell adhesion molecules. The nectin family includes four members, nectin-1–4, which are encoded by PVRL1–4 genes, respectively [11, 12]. Nectins regulate various cellular functions, such as cell adhesion, movement, proliferation, polarization, survival, and differentiation, by interacting with various proteins [11, 12]. In contrast to cadherins, nectins are able to *trans*-interact both homophilically and heterophilically **(Fig.1B)**. In addition, their heterophilic *trans*-interactions are much stronger than their homophilic *trans*-interactions [11-14]. Because of these unique properties, nectins play important roles in mediating asymmetric homotypic and heterotypic cell–cell adhesions in addition to functioning in homotypic cell–cell adhesion. Nectin first forms a *cis*-dimer and then a *trans*-dimer during cell–cell junction formation. Binding specificity of nectins is attributed to the first Ig-like loop of the extracellular domain, which is necessary and sufficient for the formation of *trans*-

dimers [13, 15]. Nectin molecules associate with various molecules via their cytoplasmic PDZ domain, such as afadin, PAR-3, MUPP1, and PATJ. Afadin binds to many proteins, such as Rap1, α-catenin, p120 catenin, PLEKHA7, and ZO-1 [16]. During the formation of cell–cell junctions, it has been suggested that nectins initially form cell–cell adhesions and then recruit cadherins to nectin-based cell–cell adhesion sites through cytoplasmic interactions to accelerate cadherin-dependent junction formation **(Fig.1C)**. Although both afadin and α-catenin are essential for the associations of nectins and cadherins, the underlying mechanism of how the nectin-afadin system is associated with the cadherin-catenin system remains unknown [11, 12]. Recent study reported that cadherins control nectin recruitment into AJs through actin clustering [17]. These observations suggest that both actin bundle formation and adhesion complex clustering mutually regulate cell–cell junction formation. How adherens junctions recruit nectins and cadherins is an important subject for future research.

Cooperative mechanism of nectins and cadherins in recognition between axons and dendrites

Nectins and cadherins cooperatively regulate both cell–cell junction formation and recognition processes. These cooperative mechanisms allow cells to achieve complex cell recognition and adhesion processes that cannot be achieved via a single mechanism. During neural development, nectin-1 and -3 play a role in the selective association of axons and dendrites in synaptogenesis by cooperating with cadherin systems [18]. Formation of the contacts between axons and dendrite involves cadherin activities. Cadherin-catenin complexes accumulate at early axon–dendrite contacts and are retained in many of the mature synapses. However, in many neurons such as hippocampal pyramidal neurons, other types of contacts are not stabilized, such as dendrite–dendrite contacts **(Fig.1D)**. In mossy fiber terminals of the hippocampus, nectin-1 is predominantly localized in the presynaptic membrane, and nectin-3 is localized in the postsynaptic membrane [19]. A heterophilic *trans*-interaction occurs between nectin-1 in axons and nectin-3 in dendrites, this interaction enhances the accumulation of cadherins at axon–dendrite contacts and stabilizes the contacts **(Fig.1C, Middle)** [20]. Mislocalization of nectin-1 to dendrites induces atypical dendrite-dendrite associations and perturbs neurite patterning **(Fig.1D)**. Nevertheless, overexpression of cadherins alone is not sufficient to induce the axon–dendrite interactions or aberrant neurite association [20]. These observations demonstrate that cadherins alone cannot initiate

such specialized local adhesion contacts. Rather, local cadherin-based contacts are formed by cooperation with the heterophilic adhesion between nectin-1 and -3 that are distributed differentially between axons and dendrites. A recent study has implicated ZO-1 in dendrite–dendrite recognition cooperatively with nectin and cadherin systems in cultured hippocampal neurons [21]. ZO-1 is involved in signal transduction at cell–cell junctions and binds to both α-catenin and afadin [22, 23]. Thus, ZO-1 might be involved in the association of nectin and cadherin. Future studies are required to examine how cell adhesion and intracellular signaling integrate and translate into cell behavior during neurite recognition processes.

Cell-cell recognition and mosaic cellular patterning in the auditory epithelium

Sensory epithelia of the ear, nose, and eye have elaborate cellular patterns, which arise as parts of the central nervous system. The basic structures and functions of sensory epithelia are the most highly conserved in evolution, not only from one vertebrate to another, but also between vertebrates and invertebrates. Within each sensory epithelium, sensory neurons or neuron-like cells, which act as transducers, convert signals from the outside into an electrical form that can be interpreted by the nervous system. In the ear,

the sensory cells are auditory hair cells. In the nose, sensory cells are olfactory sensory neurons and, in the eye, the sensory cells are photoreceptors. Each sensory cell type has a specialized structure at their apical surface, which detects an external stimulus and converts it to a membrane potential. Interestingly, the sensory cells are always separated from adjacent sensory cells by supporting cells to form alternating mosaic patterns in the sensory epithelium [12]. These mosaic patterns of sensory epithelia have also been conserved in evolution among a wide range of species. How the mosaic patterns develop and are maintained is not well understood, but recent studies suggest that nectins and cadherins play a key role.

The auditory epithelium of the mammalian inner ear (the organ of Corti) contains mechanosensory hair cells and non-sensory supporting cells **(Fig.2A)**. The hair cells are arranged in ordered rows, and each hair cell is separated from one another by a supporting cell, forming an alternating mosaic in a checkerboard-like fashion. The Notch pathway is involved in development of the auditory epithelium, and determination of cell fates occurs via lateral inhibition [24]. During development, hair cells express Notch ligands Jagged2 and Delta1, and supporting cells express Notch1. Genetic deletion of Jagged2 leads to overproduction of hair cells, but only partially disrupts the cellular

pattern [25]. These results suggest that other mechanisms may also regulate the cellular pattern formation in addition to lateral inhibition. In the developing auditory epithelium, hair and supporting cells continue to change their position and alignment beyond the period of terminal mitoses [26], indicating that cellular rearrangements also play a role in the cellular pattern formation. Cell rearrangements require dynamic coordination between cell–cell recognitions, adhesions, and movements. The differential adhesion hypothesis proposes that differential adhesion between cells promotes cell rearrangements and sorting in cell aggregates [9]. Cadherins are thought to be the main driver of these morphogenetic events. However, the mosaic cellular pattern cannot be achieved by the homophilic adhesive property of cadherins alone. In the developing mouse auditory epithelium, nectin-1 and -3 are complementarily expressed in hair and supporting cells, respectively [27]. Molecular interactions occur between nectin-1 on hair cells and nectin-3 on supporting cells, and the majority of these molecules are recruited to heterophilic binding sites. These biased cell–cell adhesions contribute to the checkerboard-like pattern formation [27]. Genetic deletion of nectin-1 or -3 disrupts the mosaic cellular pattern, inducing aberrant attachment between hair cells. The numbers of differentiated hair and supporting cells are not altered in nectin knockout (KO) mice. Thus, the Notch pathway functions normally in these KO mice. In vitro studies indicate

that heterophilic interactions of nectins are sufficient for mosaic cellular patterning [18, 27]. Upon coculture of cells expressing nectin-1 or -3, the cells rearrange themselves to form a mosaic pattern. Thus, during development, supporting cells express Notch1 and nectin-3 that heterophilically interact in *trans* with Jagged2, Delta1, and nectin-1 expressed in hair cells to establish and maintain the checkerboard-like cellular pattern in the auditory epithelium.

Cooperative mechanism of nectins and cadherins in mosaic cellular patterning of the olfactory epithelium

Another example of a characteristic cellular pattern is seen in the olfactory epithelium **(Fig.2B)**. The olfactory epithelium located in the nasal cavity is involved in odor perception. The olfactory system is thought to be an evolutionarily ancient sensory system [28]. Olfactory receptor neurons (olfactory cells) are replaced by regeneration throughout life, however the characteristic cellular pattern are maintained. The cellular pattern formation processes in the developing olfactory epithelium are unlike those in the developing auditory epithelium. Cellular patterning in the olfactory epithelium is accompanied by cellular rearrangement controlled through cooperative interactions of

nectins and cadherins [29]. In the apical surface of the olfactory epithelium in mammals, small and round-shaped olfactory cells are separated and surrounded by polygonal-like supporting cells in a characteristic mosaic pattern [30, 31]. Olfactory cells express nectin-2 and N-cadherin, while supporting cells express nectin-2, nectin-3, N-cadherin, and E-cadherin. Although olfactory and supporting cells express different types of cadherins, these cells are not segregated but rather intermingled with each other in the olfactory epithelium [29, 31]. During development, as many as half of the olfactory cells first attach to each other. As development progresses, olfactory cells separate from one another and each becomes completely surrounded by supporting cells **(Fig.2C)**. Live imaging has revealed that olfactory cells, which initially adhere to each other, are gradually separated by intercalations of supporting cells **(Fig.2D, Upper)** [29]. These observations suggest that mosaic cellular patterning may be the result of continuous intercalation of these cells. For pattern establishment during development, nectin-2 on olfactory cells and nectin-3 on supporting cells interact heterophilically and recruit N-cadherin at the junctions between olfactory and supporting cells through α-catenin **(Fig.2D, Lower)**. Differential distributions of N-cadherin lead to the intercalation of supporting cells into attached olfactory cells. Then, new junctions are generated between supporting cells and E-cadherin that exclusively accumulates in the junctions. In the

cooperation between nectins and cadherins, α-catenin is essential for recruitment of cadherin-catenin complexes at the heterophilic interfaces between olfactory and supporting cells [29]. In the olfactory epithelium of αN-catenin KO mice, N-cadherin is not efficiently recruited at the junctions between olfactory and supporting cells, resulting in failure of the separation of attached olfactory cells. In vitro studies indicate that the cadherin-catenin complex is always highly concentrated at heterophilic nectin interfaces, and that cadherin-deficient nectin transfectants fail to form stable contacts between cells and exert the effects of the heterophilic nectin interaction for mosaic cellular patterning [29]. These observations indicate that the differential distribution of N-cadherin provides the driving force for supporting cells to intercalate between the attached olfactory cells. This notion is supported by mathematical modelling of vertex dynamics in polygonal cells [29, 32]. This model is used for the polygonal pattern in which polygons are packed in a 2-dimensional (2D) sheet and consist of many polygonal edges. By applying the relative adhesiveness at each junction in wild-type or αN-catenin KO mice to the model, the cellular patterns generated by the mathematical simulations are similar to those observed in the olfactory epithelium in these mice. In addition to the differential adhesiveness of cells, differential velocity of cell migration contributes to the cellular patterning of the olfactory epithelium [29]. Time lapse video microscopy of the olfactory

epithelium has revealed that olfactory cells migrate faster than supporting cells. Mathematical simulations more accurately reflect actual cell behavior by applying the differential mobility. In vitro observations indicate that cells expressing nectin and N-cadherin migrate faster than cells expressing nectin and E-cadherin. Although the mechanism regulating differential mobility of cells in the olfactory epithelium remains unknown, the mechanism might also regulate the dispersion of cells in various epithelia. Collectively, these findings demonstrate that the cooperative action of nectins and cadherins leads to the intercalation of supporting cells between attached olfactory cells, resulting in mosaic cellular patterning of the olfactory epithelium.

Cellular rearrangement is also regulated by anisotropic contractile activity at junctions in *Drosophila* and vertebrates [4, 5]. Yamamoto et al. [33] have shown that genetic or pharmacological inhibition of myosin II results in defects of cellular patterning in the auditory epithelium during development. During cellular rearrangements in the auditory epithelium, myosin distributions are not uniform between the junctions [33]. AJ shortening is mainly controlled by actomyosin contraction rather than by self-contraction of AJs. Differential distributions of myosin between the junctions generate local tension that lead to the junctional contraction, resulting in

cellular rearrangements. In sensory epithelia including auditory and olfactory epithelia, differential adhesiveness at each junction by cooperation between nectins and cadherins contribute to shrinkage and extension of the junction. Differential adhesiveness generated by adhesion molecules must act with other mechanisms such as actin-myosin contractility in cellular patterning of sensory epithelia. Further study will elucidate the combined mechanisms between differential adhesion and actin–myosin contractility in mosaic cellular patterning of sensory epithelia.

Mosaic cellular its pattern of sensory epithelia and physiological significance

A recent study has shown that inappropriate cellular patterning affects cellular morphogenesis [34]. In mammalian cochleae, the stereociliary bundle on each hair cell is uniformly oriented to the abneural edge of the epithelium. This polarized pattern of hair bundles is a typical example of planar cell polarity (PCP) [35]. In the auditory epithelium, upon loss of nectin-3, hair cells contact each other inappropriately, resulting in abnormal orientation and morphology of hair bundles and positioning of the kinocilium. These phenotypes are only observed in aberrantly attached hair cells. Thus, the abnormal phenotypes of hair bundles are likely due to a non-autonomous effect

depending on the heterophilic interaction between nectins. Genetic deletion of PCP components causes hair bundle misorientation. However, the localization patterns of PCP components are unaffected in nectin-3 KO mice. Similarly, genetic deletion of ciliary proteins causes hair bundle misorientation without affecting the distribution of PCP components [36, 37]. The detailed molecular mechanisms underlying the orientation and morphology of hair bundles, the positioning of the kinocilium, and the localization of PCP components remain unknown. Further studies are required to investigate the molecular mechanism that connects the mosaic cellular patterning in the auditory epithelium and the morphogenesis of hair cells.

As mentioned above, the mosaic patterns of sensory epithelia have been conserved during evolution among a wide range of species. In developing sensory epithelia, supporting cells might mediate diverse functions such as metabolic and physical support of sensory cells, regulation of synaptogenesis, and cellular patterning. Supporting cells share many characteristics with neuronal glial cells [38]. Glial cells in the nervous system do not participate directly in synaptic interactions or electrical signaling, although their supportive functions help define synaptic contacts and maintain the signaling abilities of neurons. Among the various functions of glial cells,

ensheathment and insulation of neurons are important functions that have high clinical relevance to disease. Glial ensheathment and insulation of neurites helps to prevent electrical currents from leaving neurons. In sensory epithelia, sensory cells are separated from each other, and the sensory cells never attach to each other. These observations suggest that supporting cells ensheath sensory cells, and that ensheathment might prevent short circuit communication between sensory cells to ensure precise sensory transduction in response to stimuli. Further studies are required to clarify the functions of supporting cells and the physiological significance of cellular mosaics in sensory epithelia.

Conclusions and perspective

In this review, we discussed the cooperative role of nectins and cadherins in cell–cell recognition and cellular pattern formation. Combinational and differential expression of nectins and cadherins between cells and the differential reaction abilities of their extracellular domains contribute to the production of characteristic cell patterns within sensory epithelia. Other cooperative mechanisms between multiple adhesive systems may exist and potentially contribute to the generation of complex cell patterns and

structures in various tissues. Indeed, a large number of molecules interact with nectins and cadherins through their cytoplasmic associated domains. Such diverse interactions are thought to mediate crosstalk between nectins, cadherins, and other cellular systems [39]. Further studies are required to identify such cooperation in cellular recognition and patterning.

The understanding of the roles of adhesion molecules in 2D cellular pattern formation of epithelia have been progressed; however, whether these adhesion molecules also regulate the formation of complex 3D structures (e.g., the layered structure of the brain) remains unknown. Recent studies have shown that complex tissues, such as the cerebral cortex, optic cup, and kidney, form by self-organization in vitro from a homogeneous population of stem cells [40, 41]. These observations suggest that the self-organization ability of cells, as revealed by in vitro experiments, also plays a role in morphogenetic processes. Such complex morphogenesis involves various multicellular interactions in a 3D context. However, it remains unclear how the cell sorting mechanisms are employed in morphogenesis in vivo. In addition, it remains unclear whether the complex cell behavior in an aggregate consisting of multiple cell types is explained by a mathematical model such as the differential adhesion hypothesis.

Elucidating the coupling mechanisms between cell-cell recognition, differential adhesion, and cellular dynamics might reveal a more detailed picture of cellular behaviors during complex organogenesis.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Acknowledgements

We thank Drs. Hisao Honda, Ken-ichi Nibu, and Akira Suzuki for helpful discussions. The authors are supported by KAKENHI Grant Numbers 15K10782, 22791599, 24791777, 25111716, 25127710, 25440107, and 26400205, and a grant from the Takeda Science Foundation.

References

[1] S. Hirano, M. Takeichi, Cadherins in brain morphogenesis and wiring, Physiol Rev 92 (2012) 597-634.

[2] W. Meng, M. Takeichi, Adherens junction: molecular architecture and regulation, Csh Perspect Biol 1 (2009) a002899.

[3] A. Nose, A. Nagafuchi, M. Takeichi, Expressed recombinant cadherins mediate cell sorting in model systems, Cell 54 (1988) 993-1001.

[4] T. Lecuit, Adhesion remodeling underlying tissue morphogenesis, Trends Cell Biol 15 (2005) 34-42.

[5] M. Takeichi, Dynamic contacts: rearranging adherens junctions to drive epithelial remodelling, Nat Rev Mol Cell Biol 15 (2014) 397-410.

[6] A. Nose, K. Tsuji, M. Takeichi, Localization of specificity determining sites in cadherin cell adhesion molecules, Cell 61 (1990) 147-155.

[7] P. Katsamba, K. Carroll, G. Ahlsen, F. Bahna, J. Vendome, S. Posy, M. Rajebhosale, S. Price, T.M. Jessell, A. Ben-Shaul, L. Shapiro, B.H. Honig, Linking molecular affinity and cellular specificity in cadherin-mediated adhesion, Proc Natl Acad Sci U S A 106 (2009) 11594-11599.

[8] U. Tepass, Adherens junctions: new insight into assembly, modulation and function, Bioessays 24 (2002) 690-695.

[9] M.S. Steinberg, M. Takeichi, Experimental specification of cell sorting, tissue spreading, and specific spatial patterning by quantitative differences in cadherin expression, Proc Natl Acad Sci U S A 91 (1994) 206-209.

[10] J.L. Maitre, H. Berthoumieux, S.F. Krens, G. Salbreux, F. Julicher, E. Paluch, C.P. Heisenberg, Adhesion Functions in Cell Sorting by Mechanically Coupling the Cortices of Adhering Cells, Science (2012).

[11] Y. Takai, W. Ikeda, H. Ogita, Y. Rikitake, The immunoglobulin-like cell adhesion molecule nectin and its associated protein afadin, Annu Rev Cell Dev Biol 24 (2008) 309-342.

[12] H. Togashi, Differential and Cooperative Cell Adhesion Regulates Cellular Pattern in Sensory Epithelia, Frontiers in Cell and Developmental Biology 4 (2016) 104.

[13] O.J. Harrison, J. Vendome, J. Brasch, X. Jin, S. Hong, P.S. Katsamba, G. Ahlsen, R.B. Troyanovsky, S.M. Troyanovsky, B. Honig, L. Shapiro, Nectin ectodomain structures reveal a canonical adhesive interface, Nat Struct Mol Biol 19 (2012) 906-915.

[14] D. Samanta, U.A. Ramagopal, R. Rubinstein, V. Vigdorovich, S.G. Nathenson, S.C. Almo, Structure of Nectin-2 reveals determinants of homophilic and heterophilic interactions that control cell-cell adhesion, Proc Natl Acad Sci U S A 109 (2012) 14836-14840.

[15] M. Yasumi, K. Shimizu, T. Honda, M. Takeuchi, Y. Takai, Role of each immunoglobulin-like loop of nectin for its cell-cell adhesion activity, Biochemical and biophysical research communications 302 (2003) 61-66.

[16] K. Mandai, Y. Rikitake, Y. Shimono, Y. Takai, Afadin/AF-6 and canoe: roles in cell adhesion and beyond, Prog Mol Biol Transl Sci 116 (2013) 433-454.

[17] R.B. Troyanovsky, I. Indra, C.S. Chen, S. Hong, S.M. Troyanovsky, Cadherin controls nectin recruitment into adherens junctions by remodeling the actin cytoskeleton, J Cell Sci (2014).

[18] H. Togashi, J. Miyoshi, T. Honda, T. Sakisaka, Y. Takai, M. Takeichi, Interneurite affinity is regulated by heterophilic nectin interactions in concert with the cadherin machinery, J Cell Biol 174 (2006) 141-151.

[19] A. Mizoguchi, H. Nakanishi, K. Kimura, K. Matsubara, K. Ozaki-Kuroda, T. Katata, T. Honda, Y. Kiyohara, K. Heo, M. Higashi, T. Tsutsumi, S. Sonoda, C. Ide, Y. Takai, Nectin: an adhesion molecule involved in formation of synapses, J Cell Biol 156 (2002) 555-565.

[20] H. Togashi, K. Abe, A. Mizoguchi, K. Takaoka, O. Chisaka, M. Takeichi, Cadherin regulates dendritic spine morphogenesis, Neuron 35 (2002) 77-89.

[21] R. Komaki, H. Togashi, Y. Takai, Regulation of Dendritic Filopodial Interactions by ZO-1 and Implications for Dendrite Morphogenesis, PLoS One 8 (2013) e76201.

[22] M. Itoh, A. Nagafuchi, S. Moroi, S. Tsukita, Involvement of ZO-1 in cadherin-based cell adhesion through its direct binding to alpha catenin and actin filaments, J Cell Biol 138 (1997) 181-192.

[23] S. Yokoyama, K. Tachibana, H. Nakanishi, Y. Yamamoto, K. Irie, K. Mandai, A. Nagafuchi, M. Monden, Y. Takai, alpha-catenin-independent recruitment of ZO-1 to nectin-based cell-cell adhesion sites through afadin, Mol Biol Cell 12 (2001) 1595-1609.

[24] M.W. Kelley, Regulation of cell fate in the sensory epithelia of the inner ear, Nat Rev Neurosci 7 (2006) 837-849.

[25] P.J. Lanford, Y. Lan, R. Jiang, C. Lindsell, G. Weinmaster, T. Gridley, M.W. Kelley, Notch signalling pathway mediates hair cell development in mammalian cochlea, Nat Genet 21 (1999) 289-292.

[26] E. McKenzie, A. Krupin, M.W. Kelley, Cellular growth and rearrangement during the development of the mammalian organ of Corti, Dev Dyn 229 (2004) 802-812.

[27] H. Togashi, K. Kominami, M. Waseda, H. Komura, J. Miyoshi, M. Takeichi, Y. Takai, Nectins Establish a Checkerboard-like Cellular Pattern in the Auditory Epithelium, Science 333 (2011) 1144-1147.

[28] H.B. Treloar, A.M. Miller, A. Ray, C.A. Greer, Development of the Olfactory System, in: A. Menini (Ed.), The Neurobiology of Olfaction, Boca Raton (FL), 2010.

[29] S. Katsunuma, H. Honda, T. Shinoda, Y. Ishimoto, T. Miyata, H. Kiyonari, T. Abe, K. Nibu, Y. Takai, H. Togashi, Synergistic action of nectins and cadherins generates the mosaic cellular pattern of the olfactory epithelium, J Cell Biol 212 (2016) 561-575.

[30] A. Cuschieri, L.H. Bannister, The development of the olfactory mucosa in the mouse: electron microscopy, Journal of anatomy 119 (1975) 471-498.

[31] A. Steinke, S. Meier-Stiegen, D. Drenckhahn, E. Asan, Molecular composition of tight and adherens junctions in the rat olfactory epithelium and fila, Histochem Cell Biol 130 (2008) 339-361.

[32] H. Honda, M. Tanemura, T. Nagai, A three-dimensional vertex dynamics cell model of space-filling polyhedra simulating cell behavior in a cell aggregate, J Theor Biol 226 (2004) 439-453.

[33] N. Yamamoto, T. Okano, X. Ma, R.S. Adelstein, M.W. Kelley, Myosin II regulates extension, growth and patterning in the mammalian cochlear duct, Development 136 (2009) 1977-1986.

[34] T. Fukuda, K. Kominami, S. Wang, H. Togashi, K. Hirata, A. Mizoguchi, Y. Rikitake, Y. Takai, Aberrant cochlear hair cell attachments caused by Nectin-3 deficiency result in hair bundle abnormalities, Development 141 (2014) 399-409.

[35] M. Montcouquiol, R.A. Rachel, P.J. Lanford, N.G. Copeland, N.A. Jenkins, M.W. Kelley, Identification of Vangl2 and Scrb1 as planar polarity genes in mammals, Nature 423 (2003) 173-177.

[36] C. Jones, V.C. Roper, I. Foucher, D. Qian, B. Banizs, C. Petit, B.K. Yoder, P. Chen, Ciliary proteins link basal body polarization to planar cell polarity regulation, Nat Genet 40 (2008) 69-77.

[37] C.W. Sipe, X. Lu, Kif3a regulates planar polarization of auditory hair cells through both ciliary and non-ciliary mechanisms, Development (2011).

[38] G. Wan, G. Corfas, J.S. Stone, Inner ear supporting cells: rethinking the silent majority, Semin Cell Dev Biol 24 (2013) 448-459.

[39] E. Stepniak, G.L. Radice, V. Vasioukhin, Adhesive and signaling functions of cadherins and catenins in vertebrate development, Cold Spring Harb Perspect Biol 1 (2009) a002949.

[40] Y. Sasai, Cytosystems dynamics in self-organization of tissue architecture, Nature 493 (2013) 318-326.

[41] A. Taguchi, Y. Kaku, T. Ohmori, S. Sharmin, M. Ogawa, H. Sasaki, R. Nishinakamura, Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells, Cell Stem Cell 14 (2014) 53-67.

Figure legends

Figure 1. Molecular interactions between nectins and cadherins.

(A) Molecular interactions between nectins and cadherins at the cell–cell junction. α, α-catenin; β, β-catenin. **(B)** Schematic illustrations of *trans*-interactions among cadherins or nectins. (Upper) Homophilic *trans*-interactions between cadherins. (Lower) Homophilic and heterophilic *trans*-interactions between nectins. **(C)** Association of the nectin-afadin system with the cadherin-catenin system during the formation of cell–cell junctions. (Upper) Homophilic *trans*-interactions between nectins recruit cadherins to the contact site by cytoplasmic interactions and promote the formation of adherens junction. (Middle) Heterophilic *trans*-interactions between nectins recruit cadherins intensely to the contact site and induce strong cell–cell adhesion. (Lower) Without α-catenin, cadherin accumulation at the contact site is decreased and the cell–cell adhesion is weakened. **(D)** Axon-dendrite recognition in hippocampal neurons. Immunostaining for dendrite marker MAP2 of cultured hippocampal neuron and schematic illustrations of dendrite morphology are shown. (Right) Control. (Left) Ectopic expression of nectin-1 to the dendrites. Adapted from [18].

Figure 2. Mosaic cellular pattern in sensory epithelia

(A) Schematic illustration of the apical surface of the mouse auditory epithelium. **(B)** Schematic illustration of the apical surface of the mouse olfactory epithelium. **(C)** Mosaic cellular pattern formations in the developing mouse olfactory epithelium from embryonic day (E) 12 to postnatal day (P) 28. The olfactory cells, which initially adhered to each other in the cluster, gradually separated. **(D)** Cellular rearrangements in the developing mouse olfactory epithelium. (Upper) Time-lapse imaging of the organ culture of the olfactory epithelium prepared on E14. Cell junctions are visualized by ZO-1-EGFP. Black and white reversal images at 60-min intervals are shown. Adapted from [29]. (Lower) Schematic illustrations of the adhesive interactions between olfactory and supporting cells during cellular rearrangements.

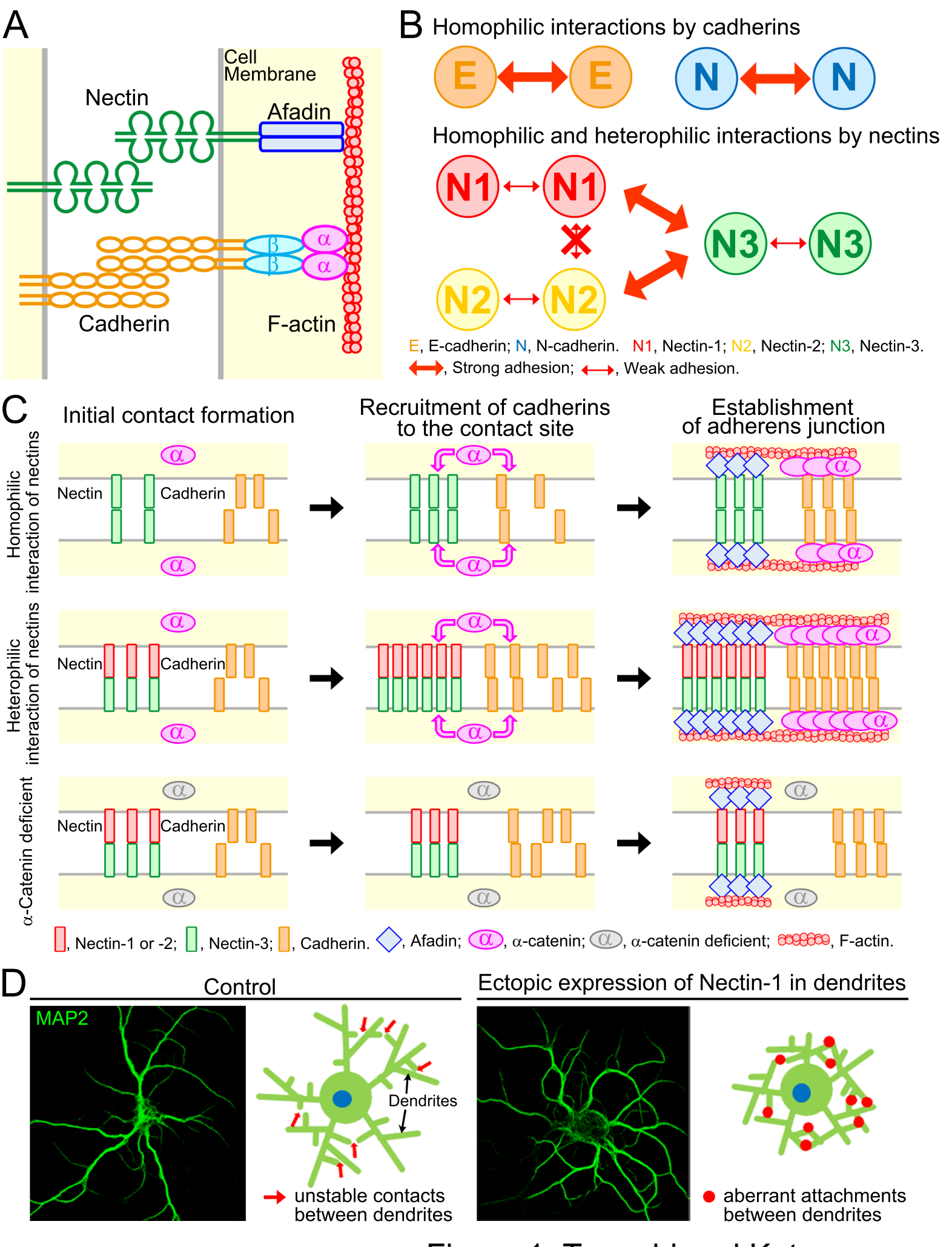

Figure 1. Togashi and Katsunuma

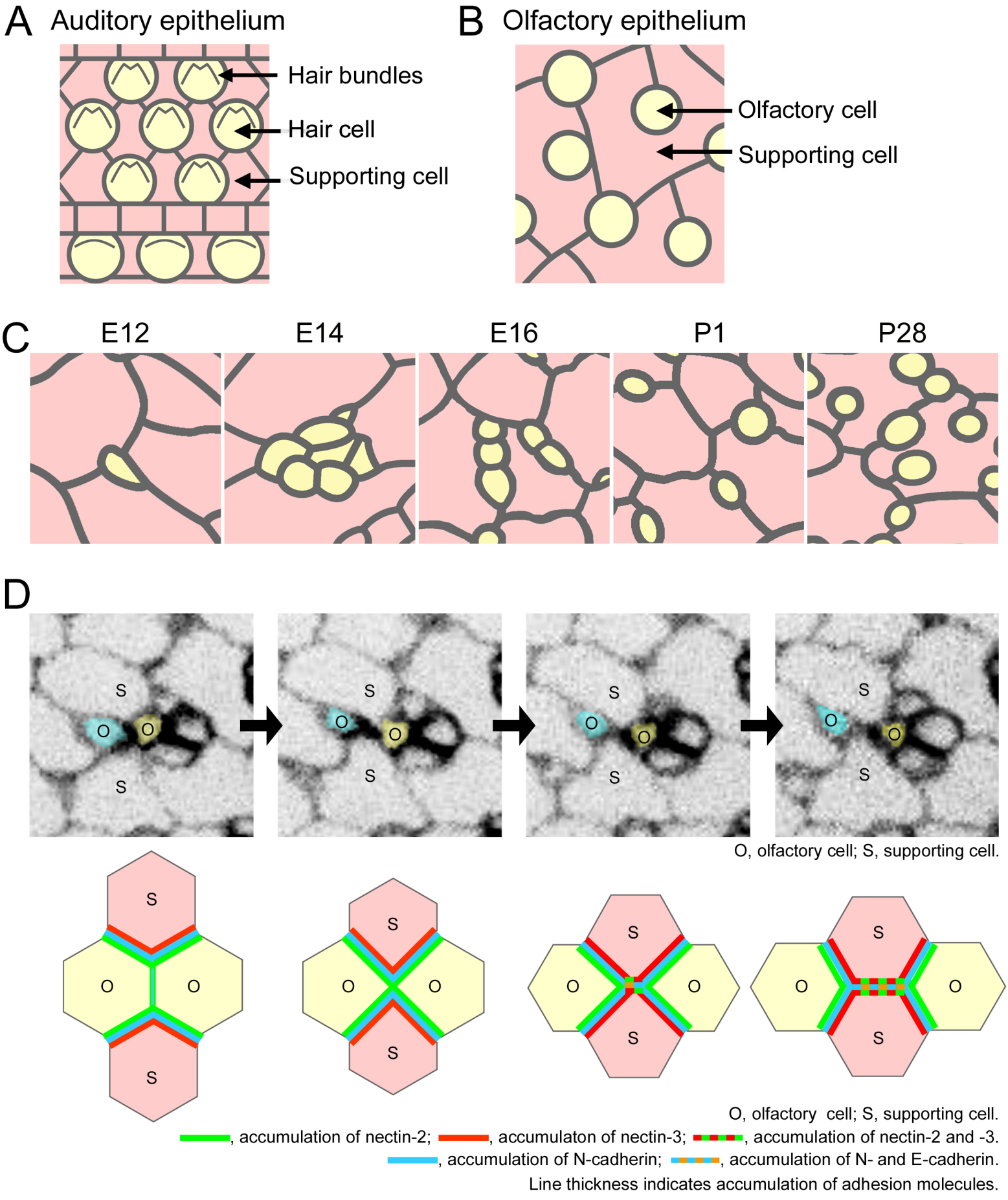

Figure 2. Togashi and Katsunuma