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2159-2

2010 Workshop on the Development of Behaviour: Emergent Properties of Nervous Systems

2 - 20 August 2010

Neurogenesis and Cell Polarity

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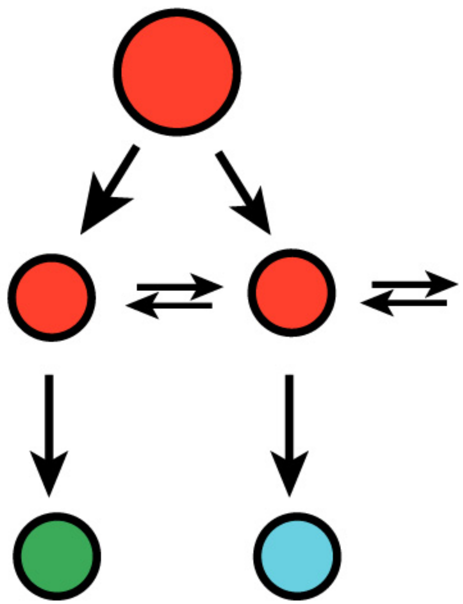
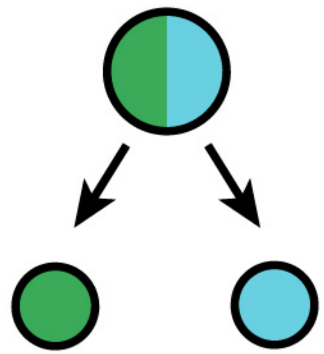
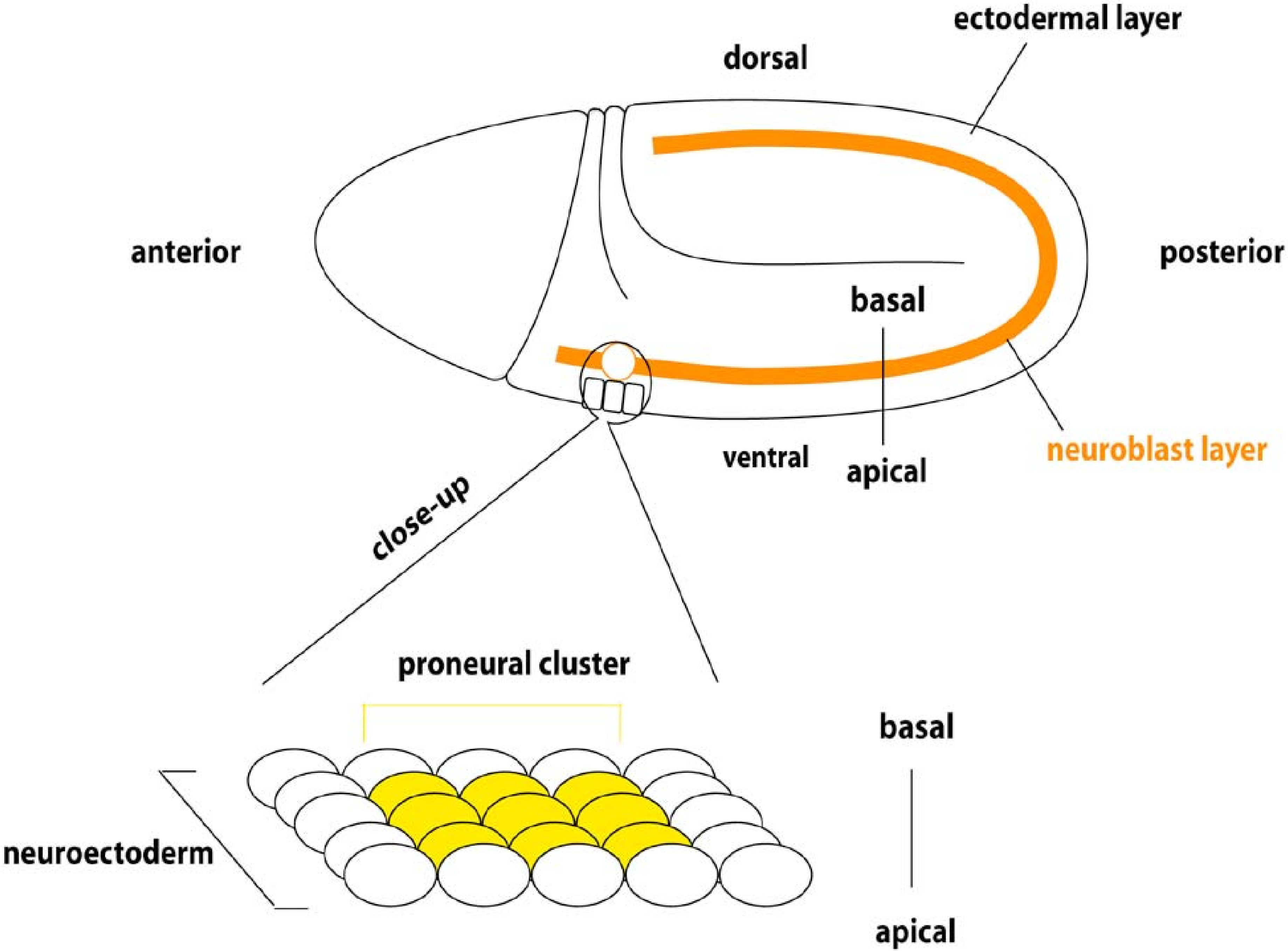
How sister cells can become different



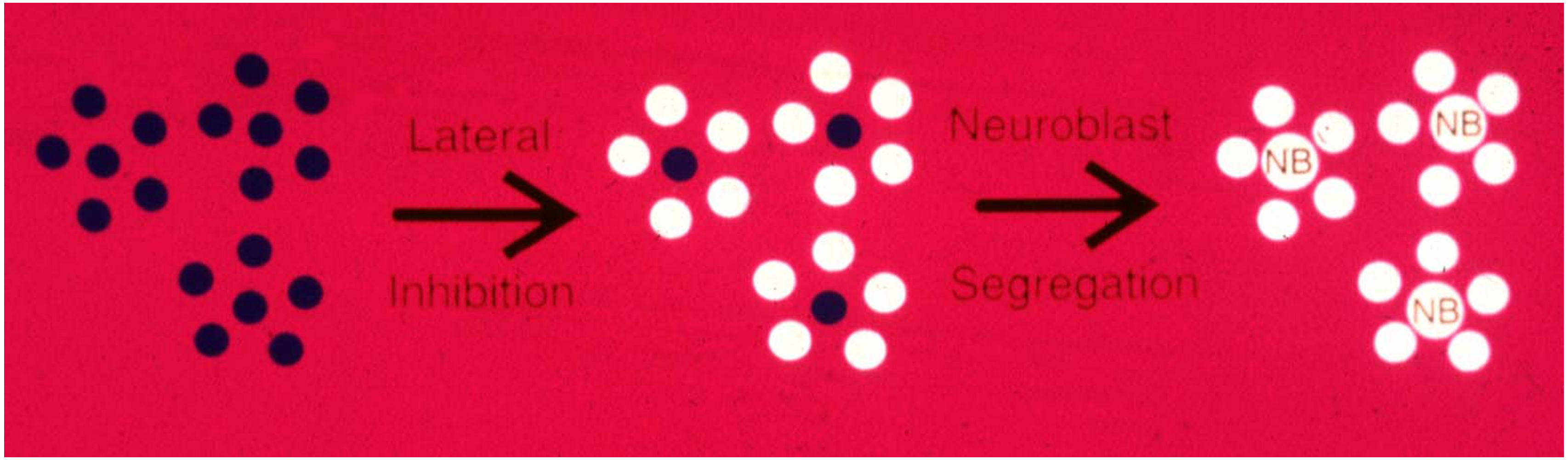
cell-cell
interaction



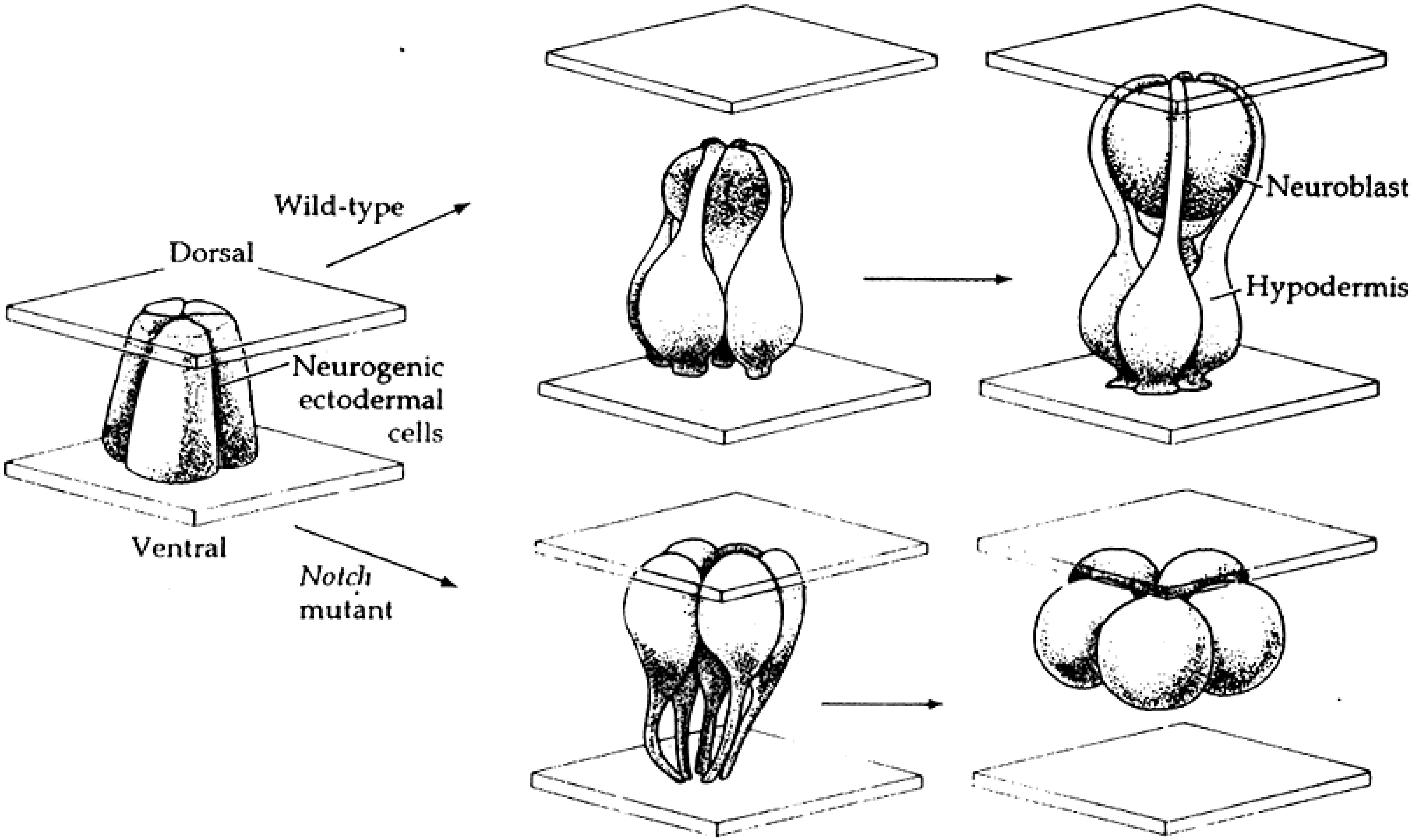
segregating
determinant

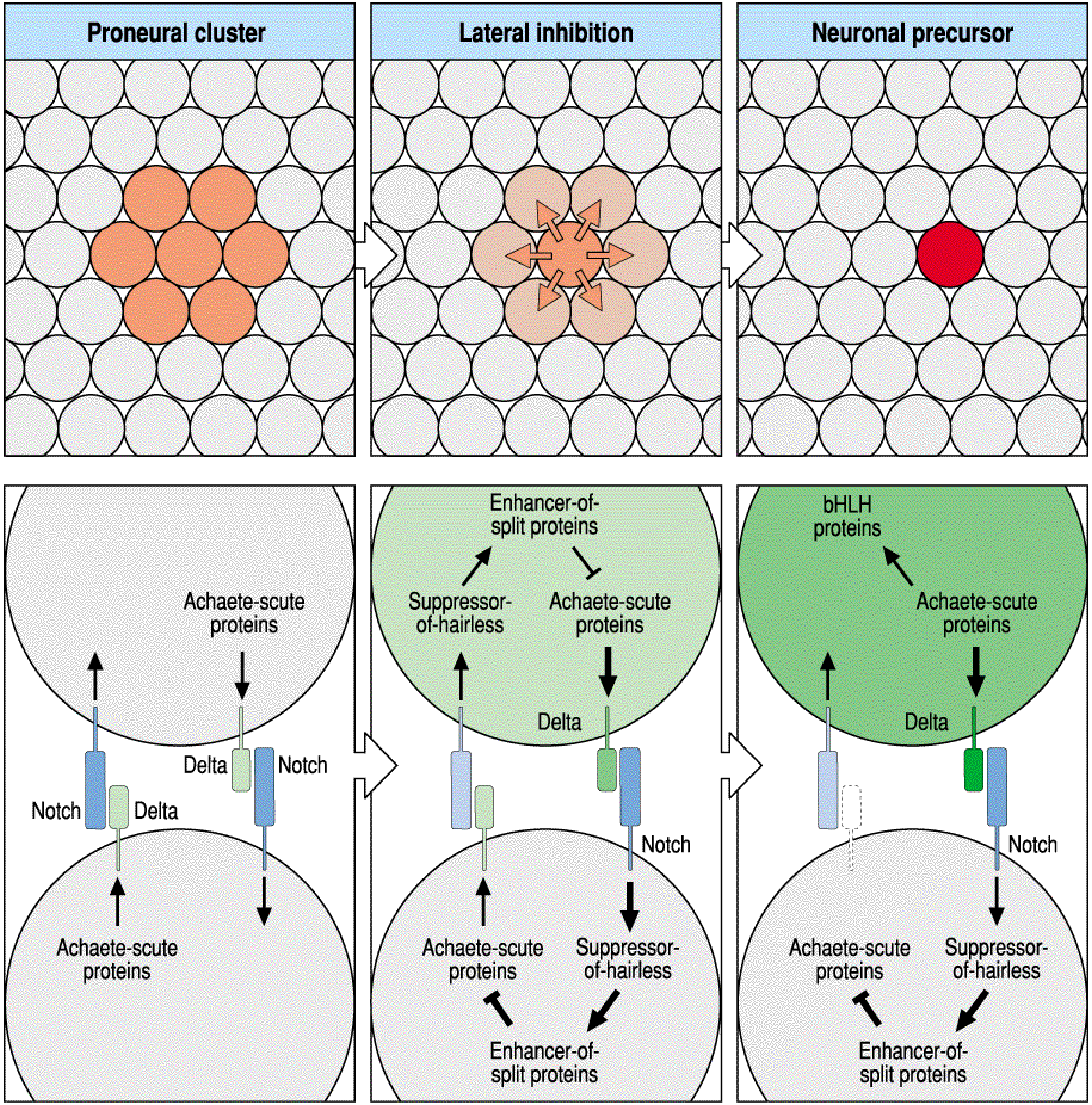

ectodermal layer
dorsal
anterior
posterior
basal
ventral
apical
neuroblast layer
close-up
proneural cluster
basal
neuroectoderm
apical

Neuroblasts segregate from clusters of
equivalent neurectodermal cells by lateral inhibition

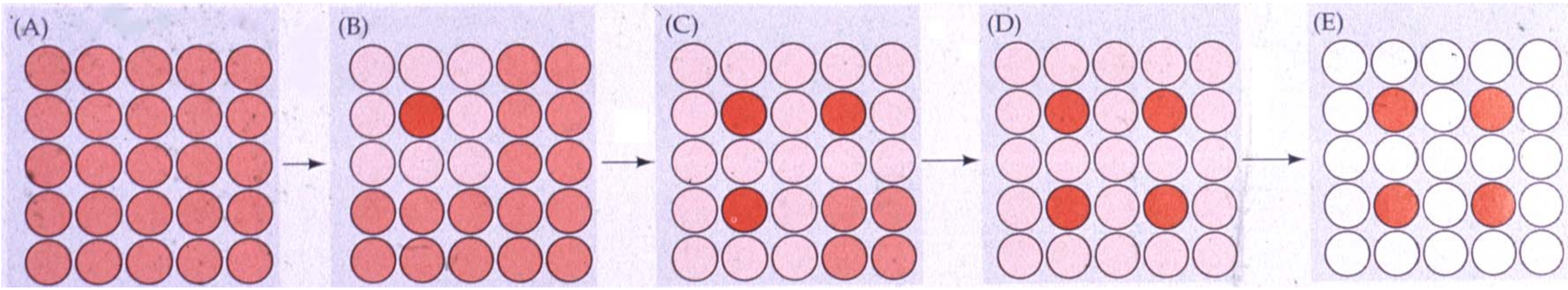


Neurogenic mutants

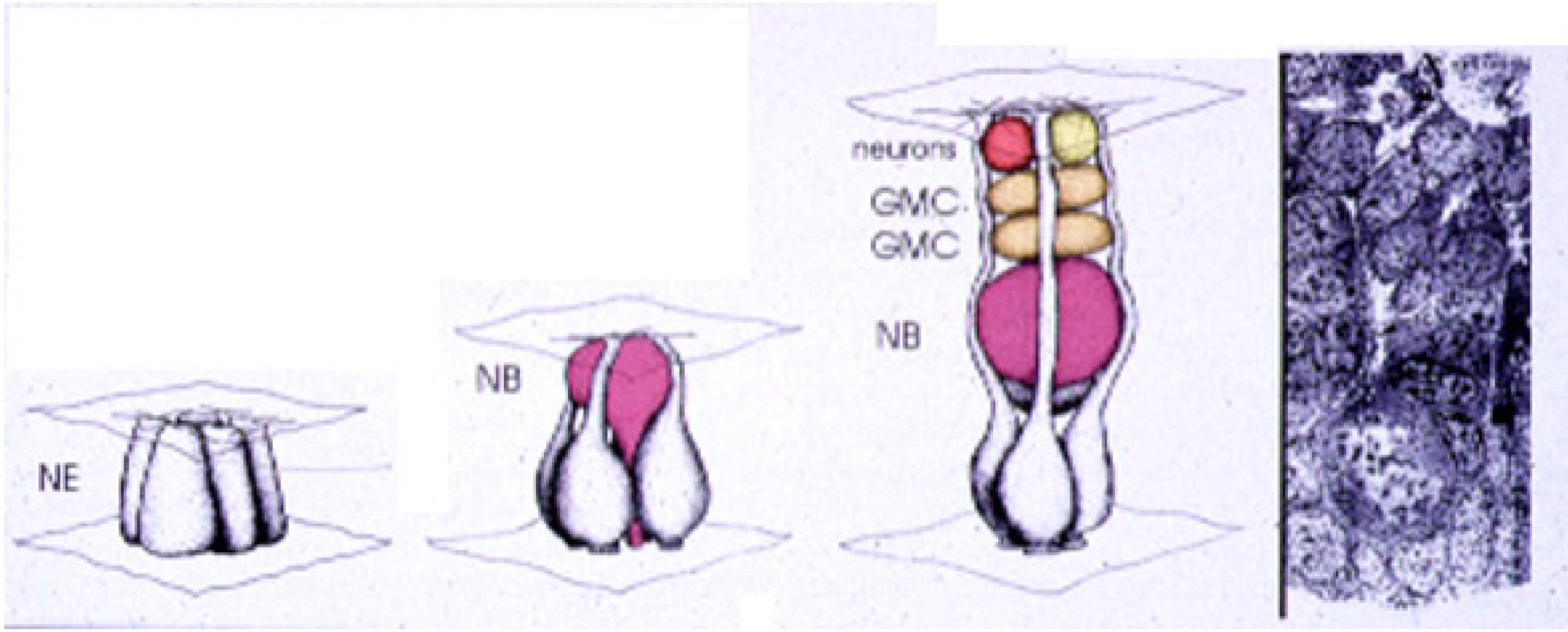



Proneural cluster
Lateral inhibition
Neuronal precursor
Achaete-scute proteins
Notch
Delta
Delta
Notch
Achaete-scute proteins
Enhancer-of-split proteins
Suppressor-of-hairless
Achaete-scute proteins
Delta
Notch
Achaete-scute proteins
Suppressor-of-hairless
Enhancer-of-split proteins
bHLH proteins
Achaete-scute proteins
Delta
Notch
Achaete-scute proteins
Suppressor-of-hairless
Enhancer-of-split proteins

Lateral inhibition in fields of equivalent cells leads to spaced patterns of different cell types



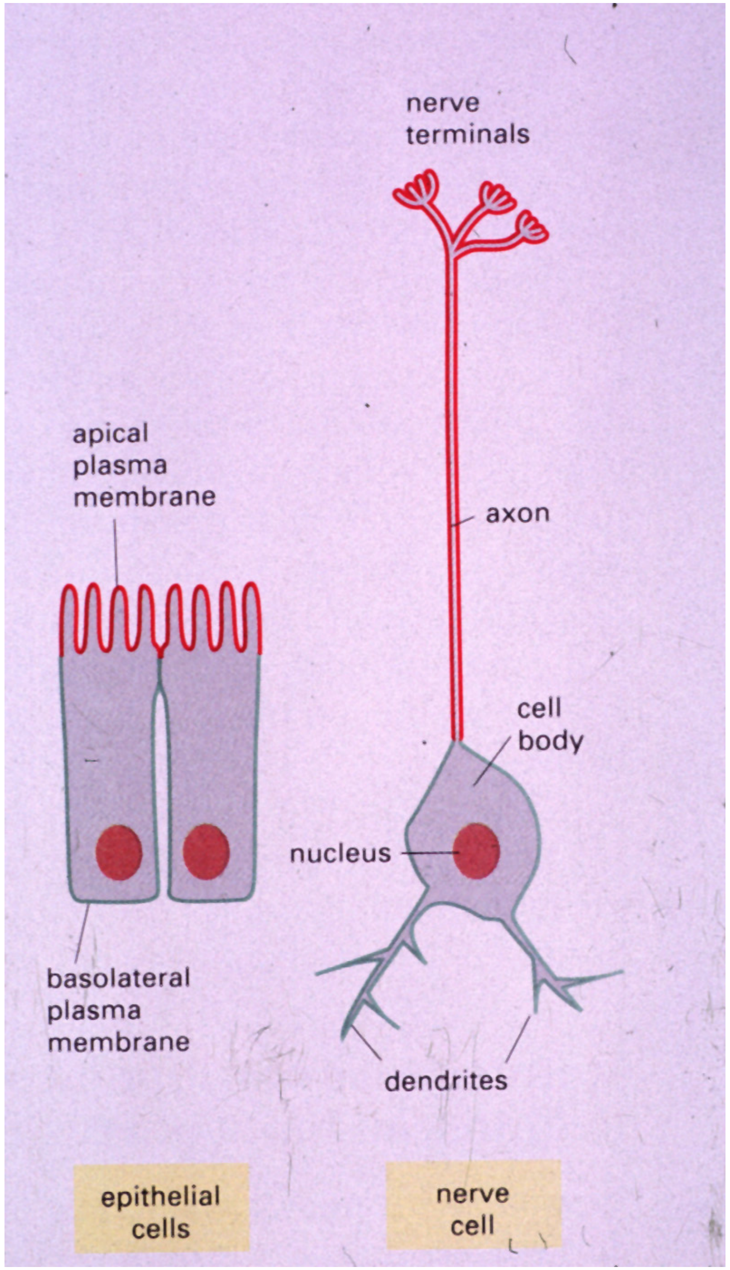
The nervous system derives from stem cells called neuroblasts



Uncommitted
neurectodemal cells

Neuroblast
segregation

Neuroblast
division produces
ganglion mother cells
….and neurons

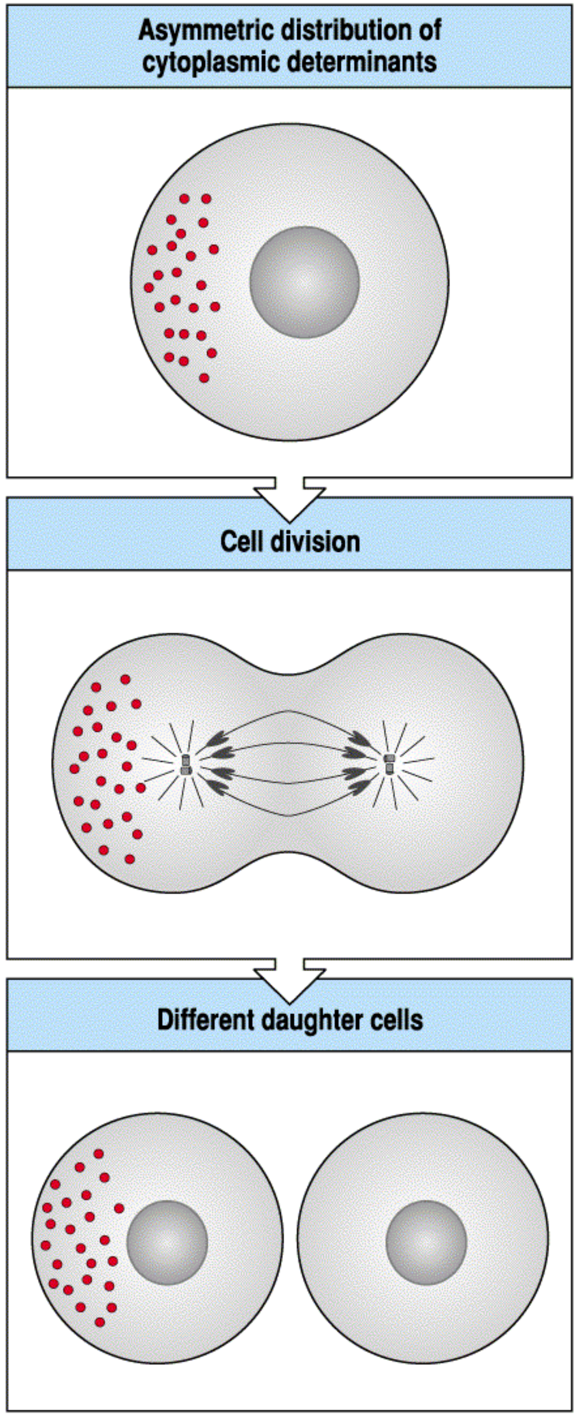

nerve
terminals
apical
plasma
membrane
axon
cell
body
nucleus
basolateral
plasma
membrane
dendrites
epithelial
cells
nerve
cell

Segregation of determinants requires:

1. The establishment of cell polarity

2. The asymmetric segregation of determinants with respect to the axis of polarity

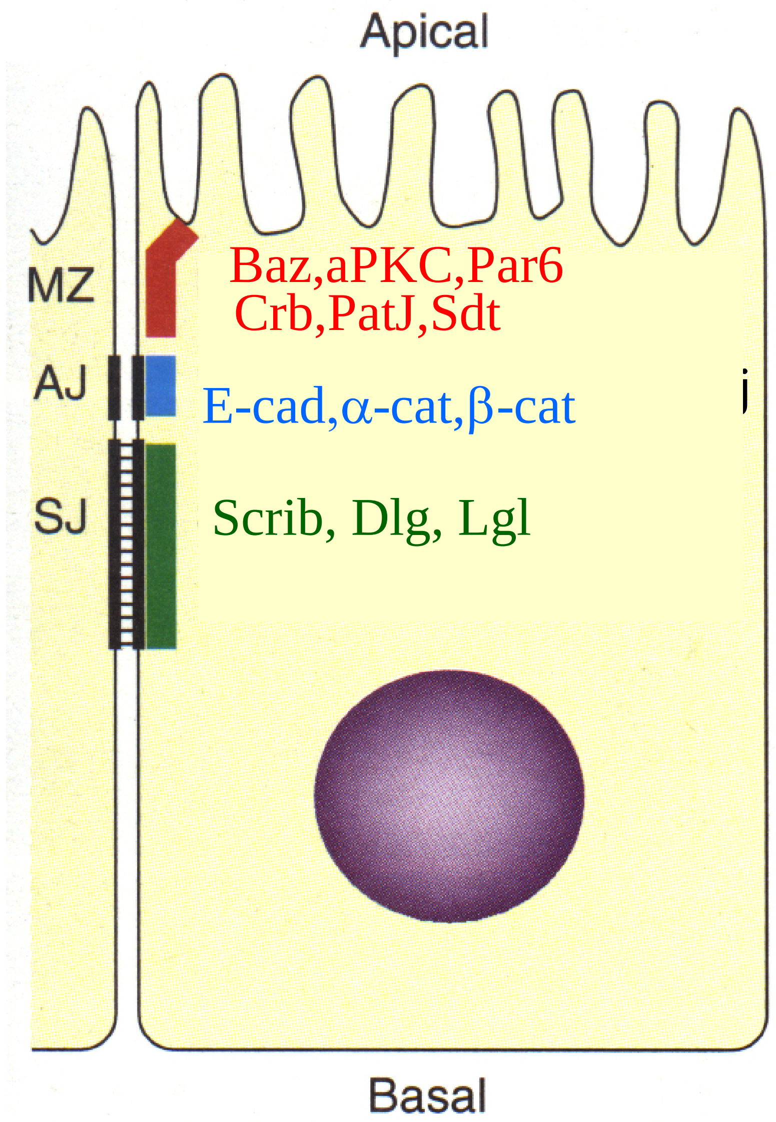
3. The orientation of cell division with respect to the segregation of determinants

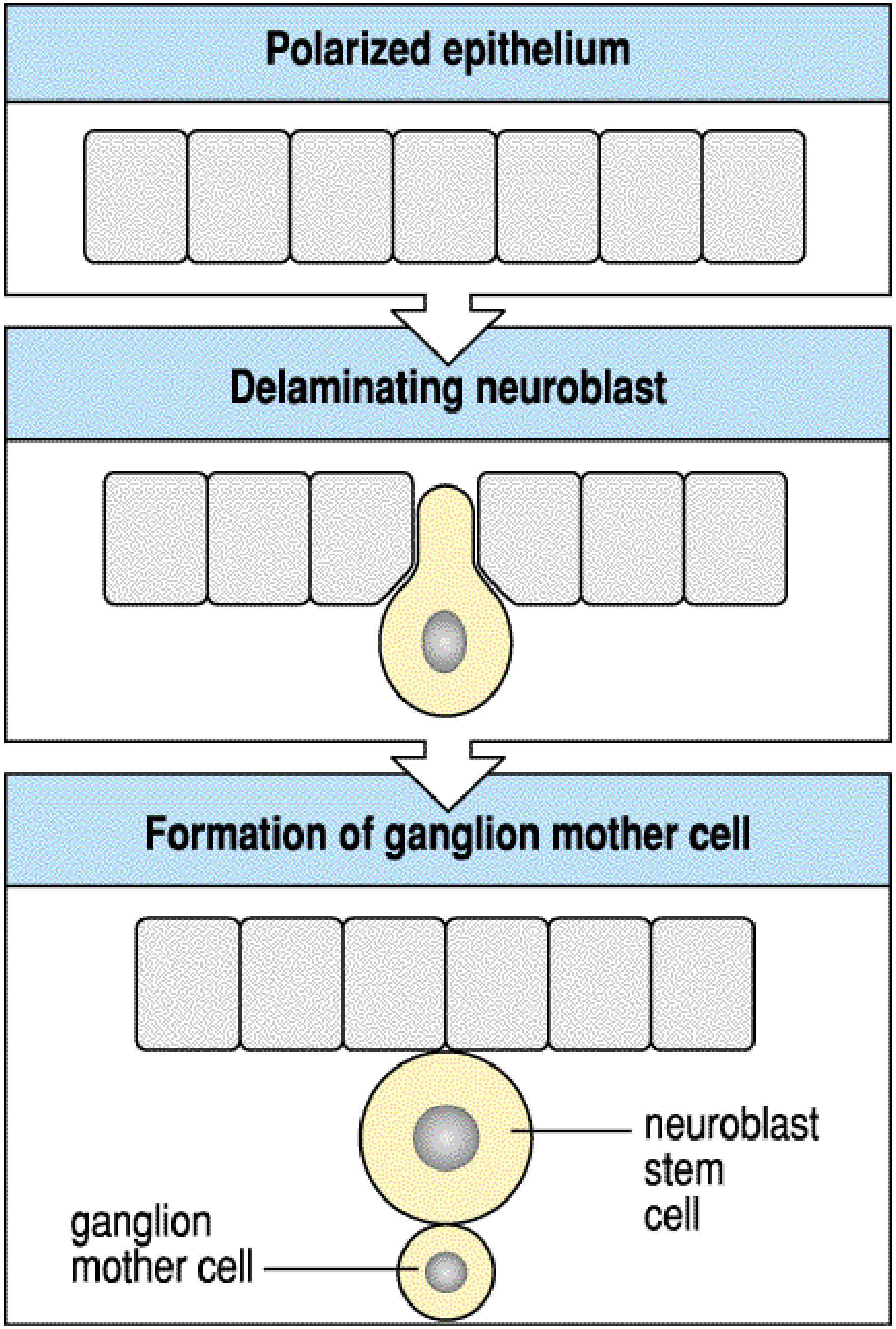


These complexes localise to specific epithelial membrane domains:

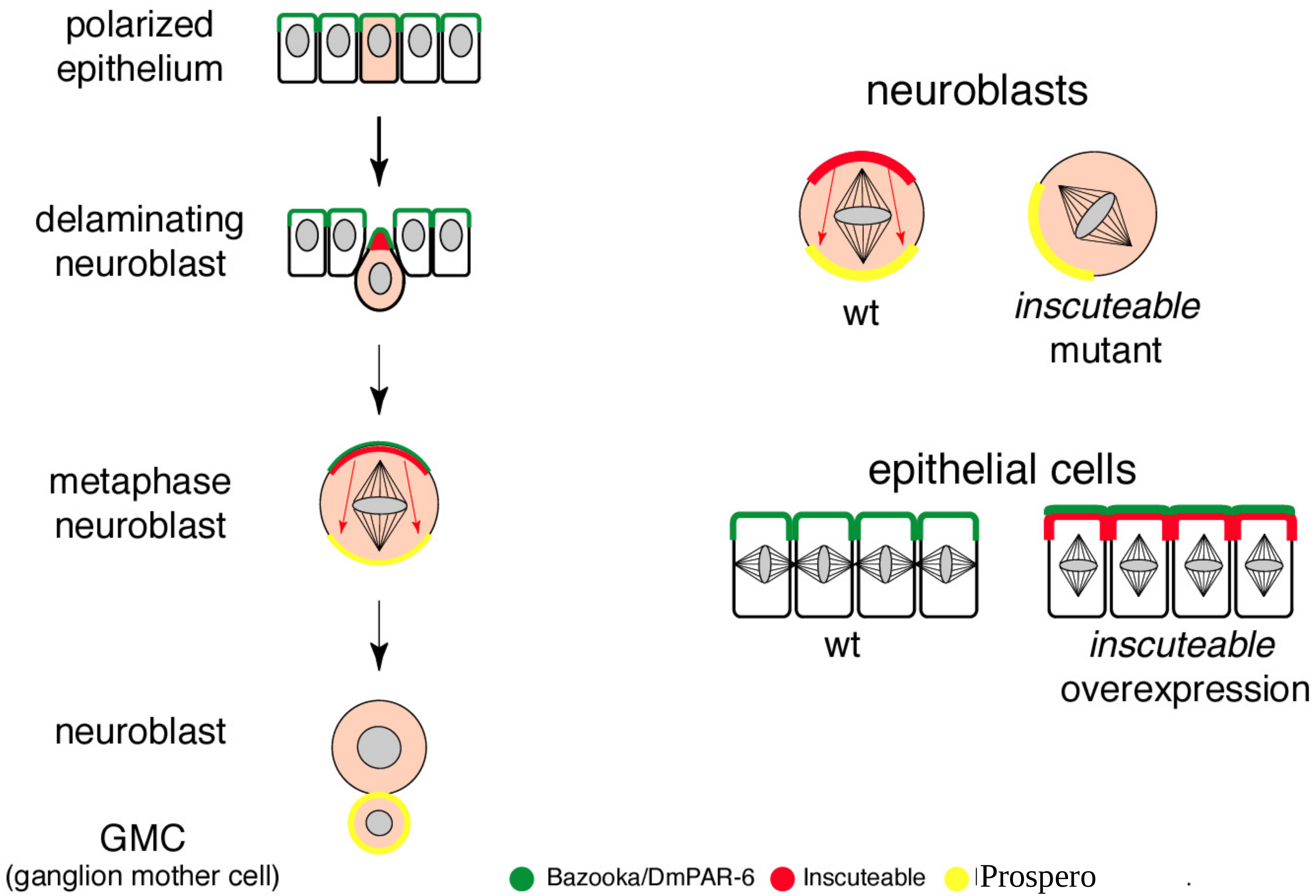
Bazooka complex
Crumbs complex
Intercellular junction

Scribbled complex




Polarized epithelium
Delaminating neuroblast
Formation of ganglion mother cell
neuroblast stem cell
ganglion mother cell

Asymmetric Cell Division in *Drosophila* neuroblasts

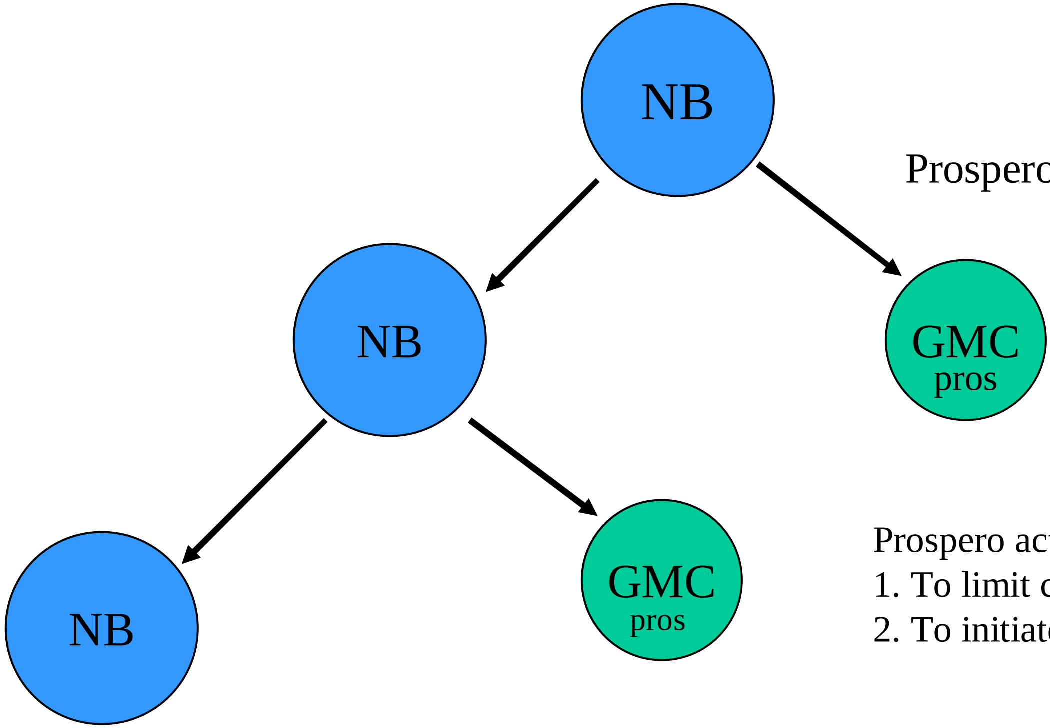


1. How are ganglion mother cells (GMCs) made different from neuroblasts (NBs)?

2. How are GMCs made different from each other?

The difference between the NB and GMC is set at <u>each</u> neuroblast division by the segregation of determinants.

One of these determinants is encoded by the gene *prospero*,
whose protein product is a transcription factor



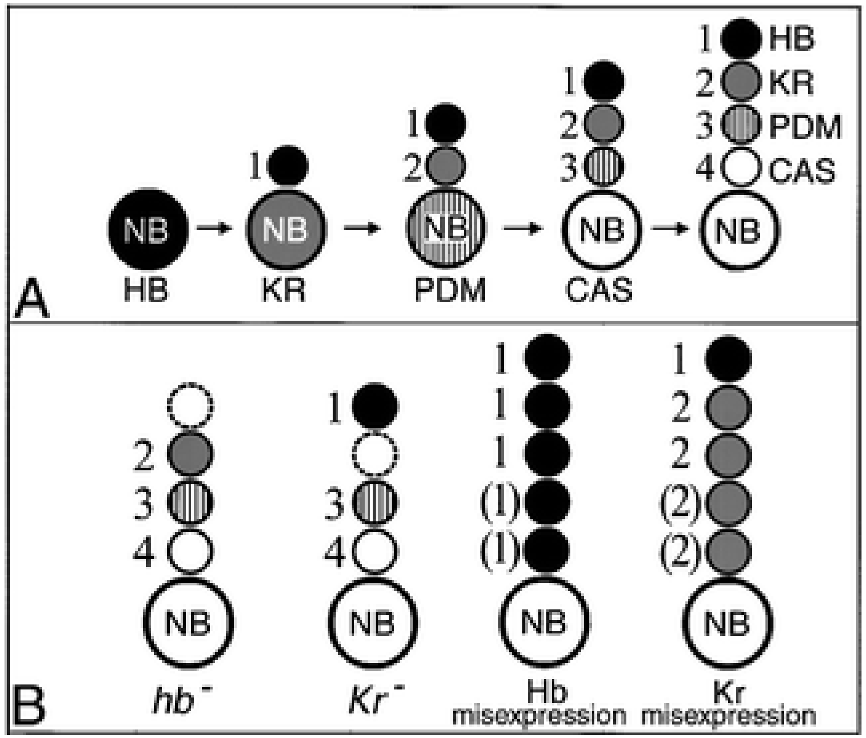
Prospero segregates only into the GMC

Prospero acts in each GMC
1. To limit cell division to just one further cycle
2. To initiate neural programmes of gene expression

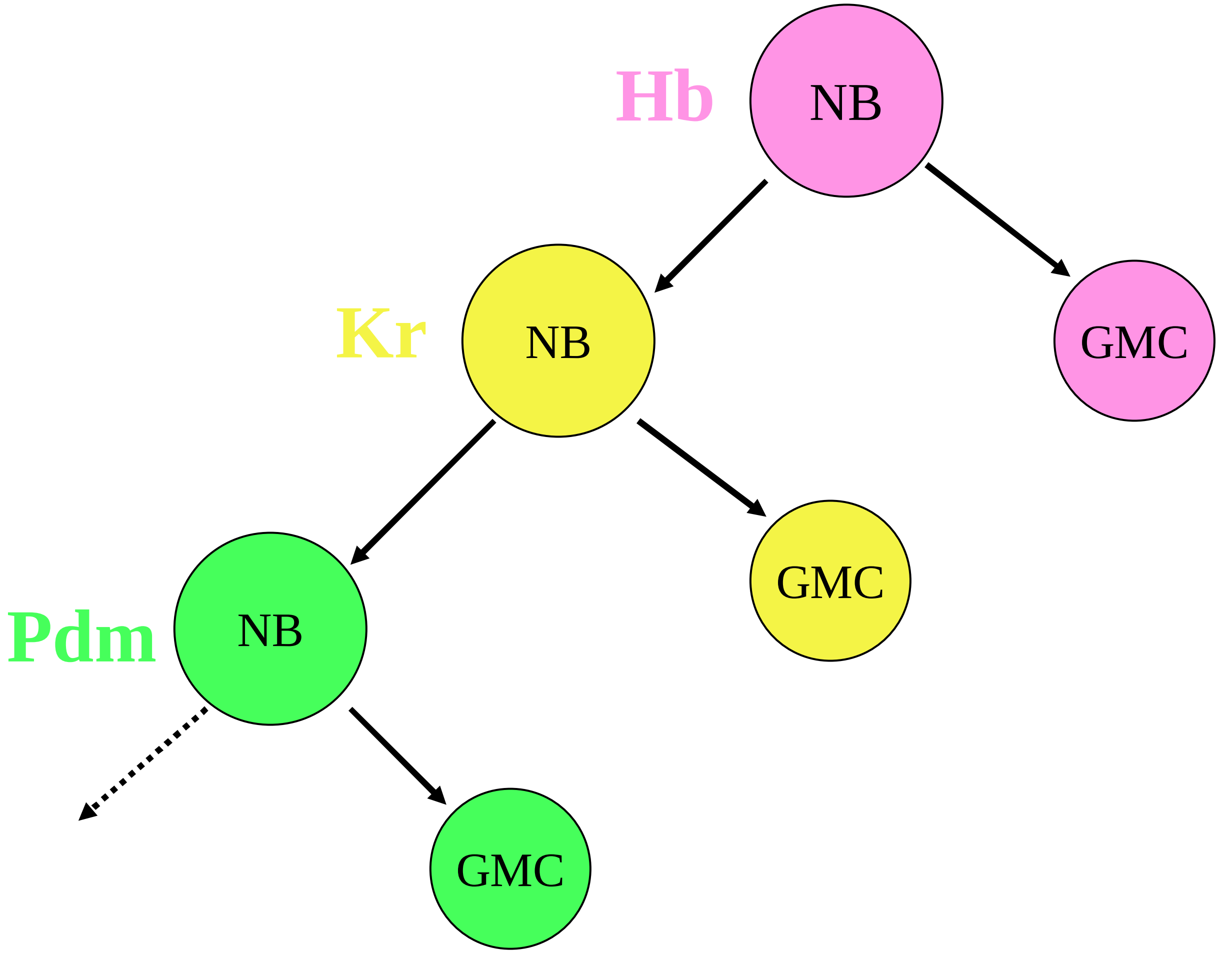
The identity of GMCs is set by the segregation of determinants that are expressed in dynamic patterns in the NBs

Wild type expression pattern: constellation of TFs expressed changes with each cell cycle

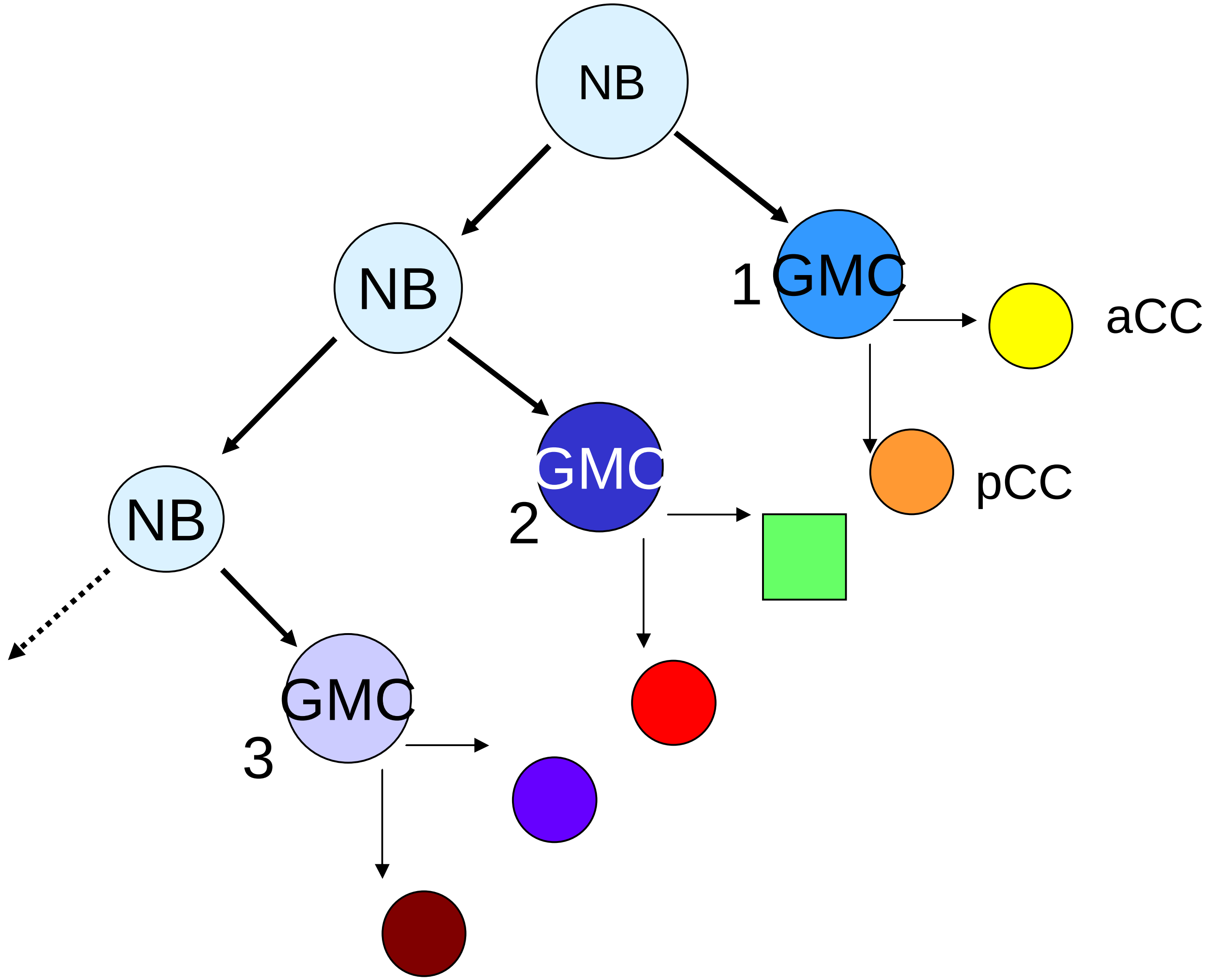
Altering the pattern of TF expression in the NB changes GMC fate

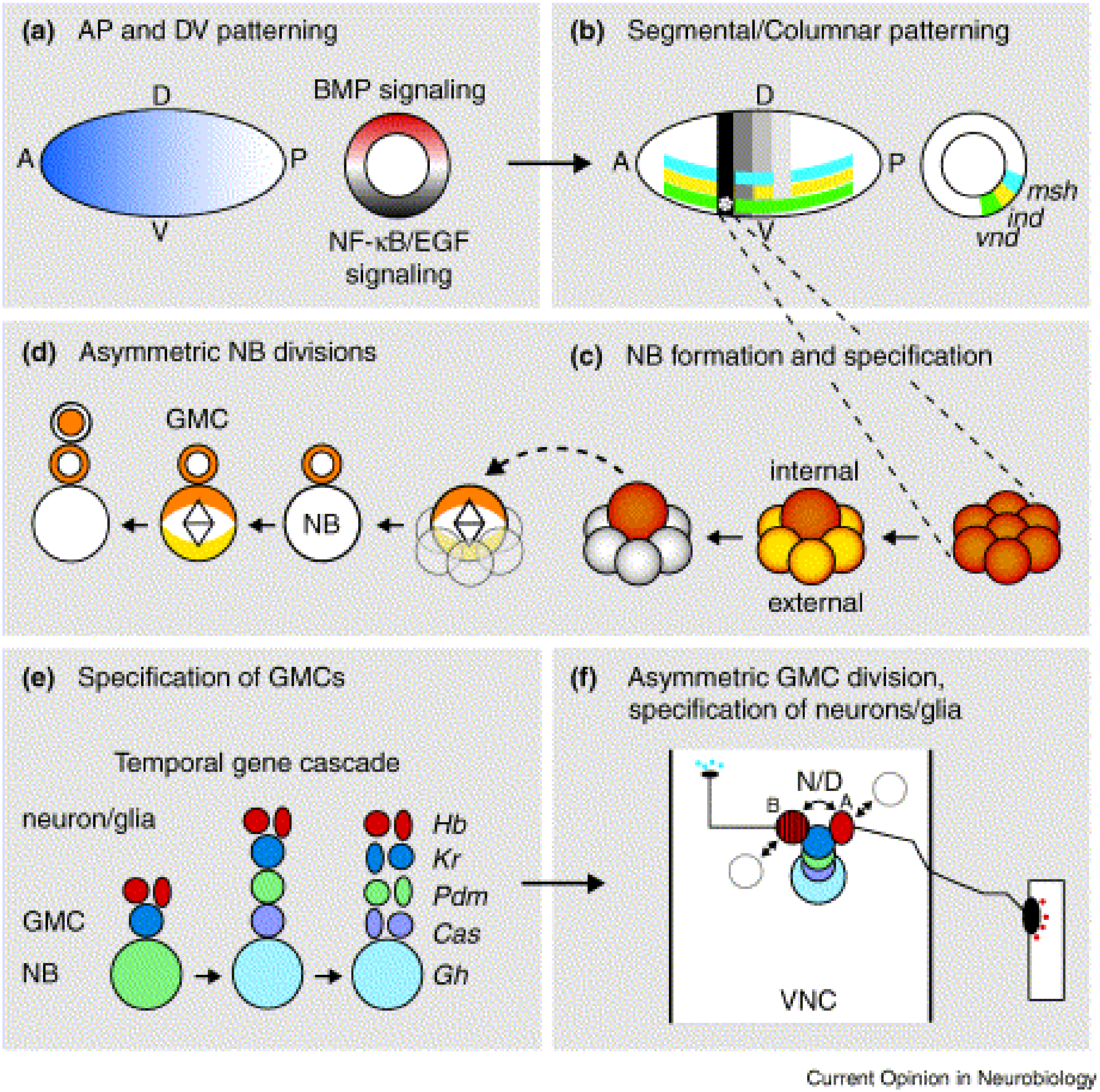


The <u>identity</u> of GMCs is set by the segregation of determinants that are expressed in a dynamic pattern, changing with every cell cycle of the parent neuroblast (NB) stem cell



How are daughters of GMCs made different from each other?





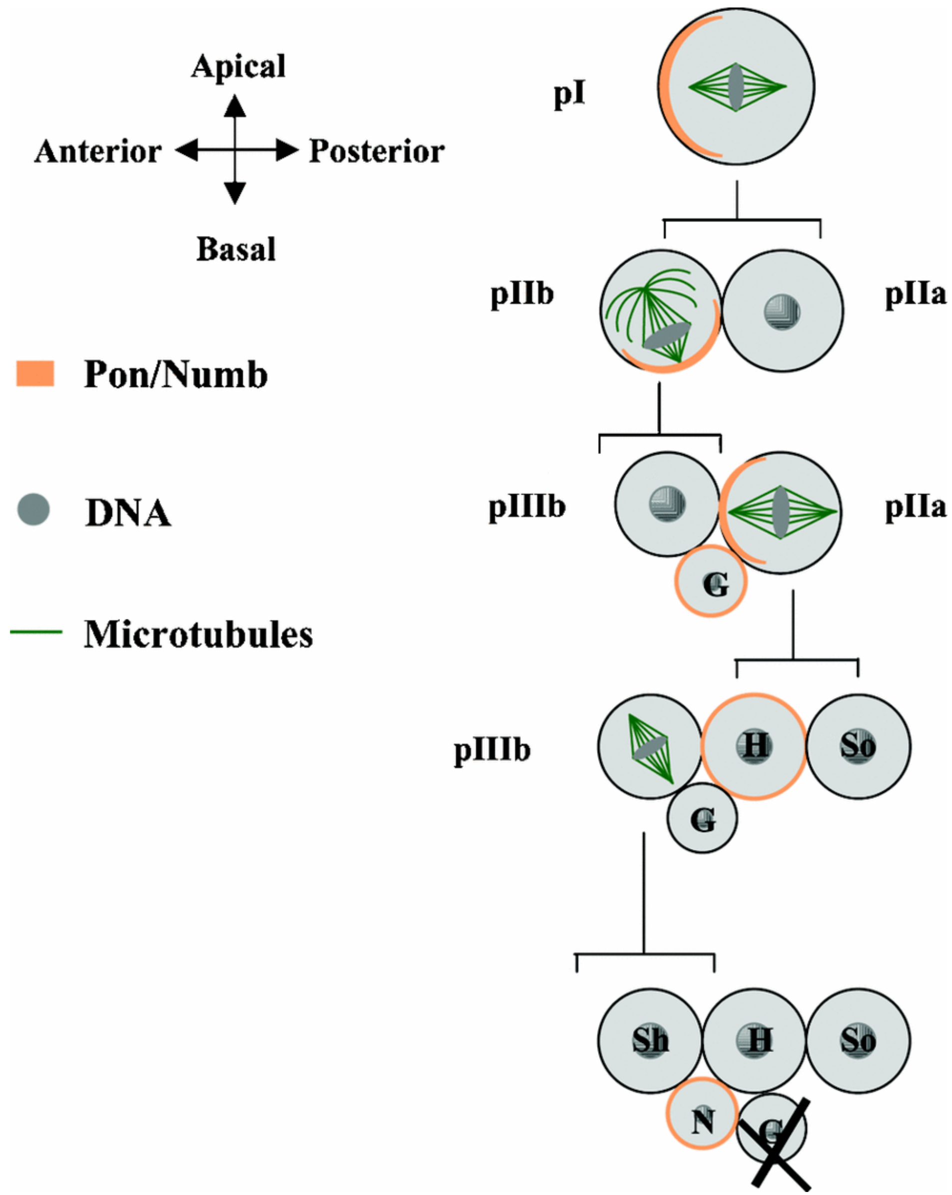
Skeath & Thor 2003
Curr.Op.Neurobiol.
13: 8-15

Is planar cell polarity important for NS development?

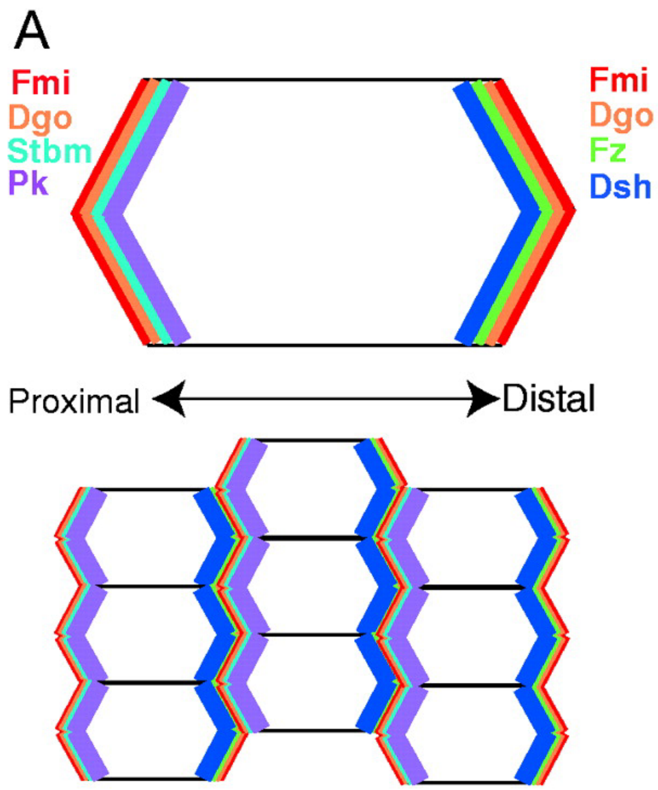
1. Sensory organ precursor division

2. Patterning in the vertebrate cochlea

Some of the asymmetric divisions that generate the peripheral (sensory) system occur in the plane of the epithelium



The products of many PCP genes are asymmetrically localised in wing cells

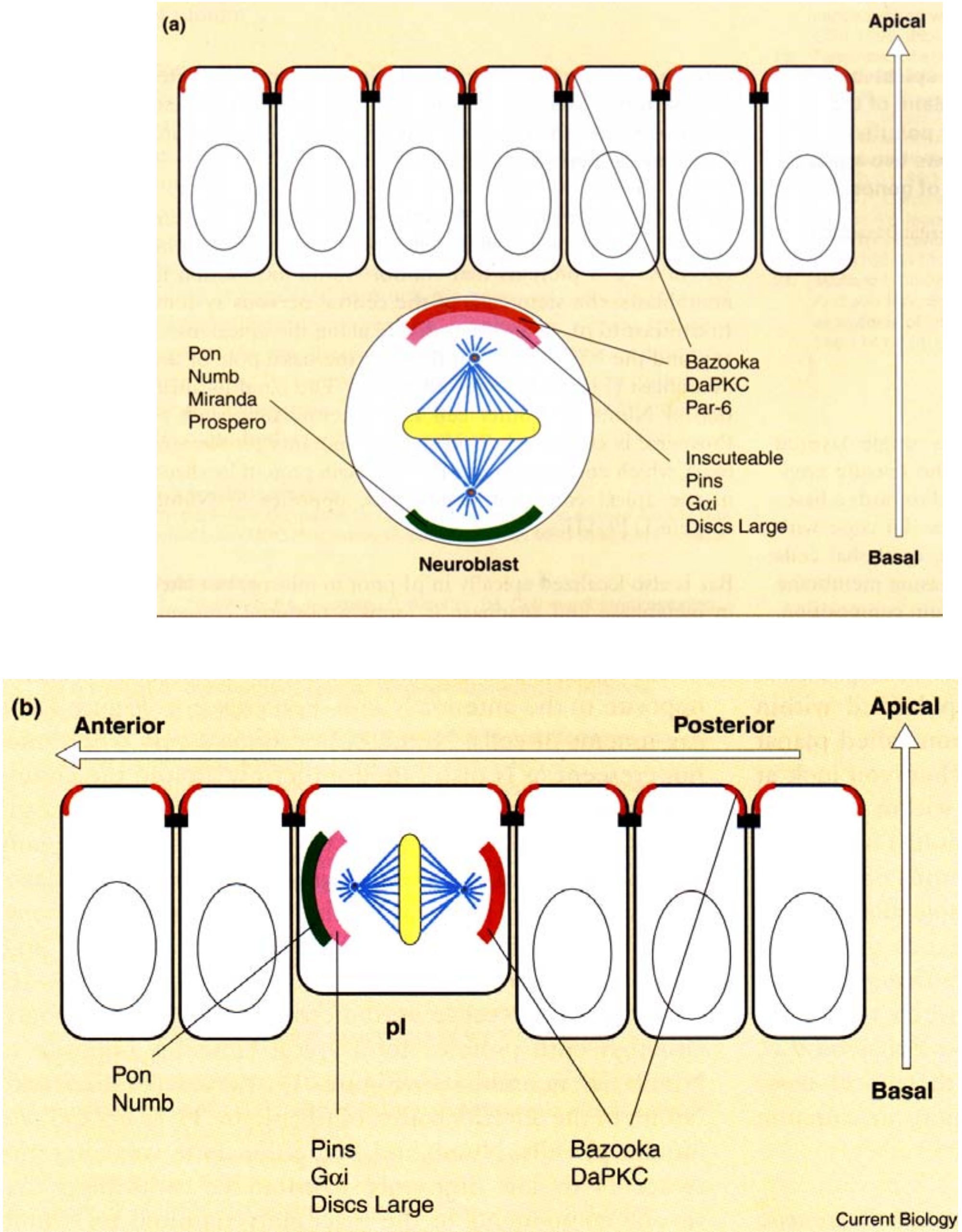


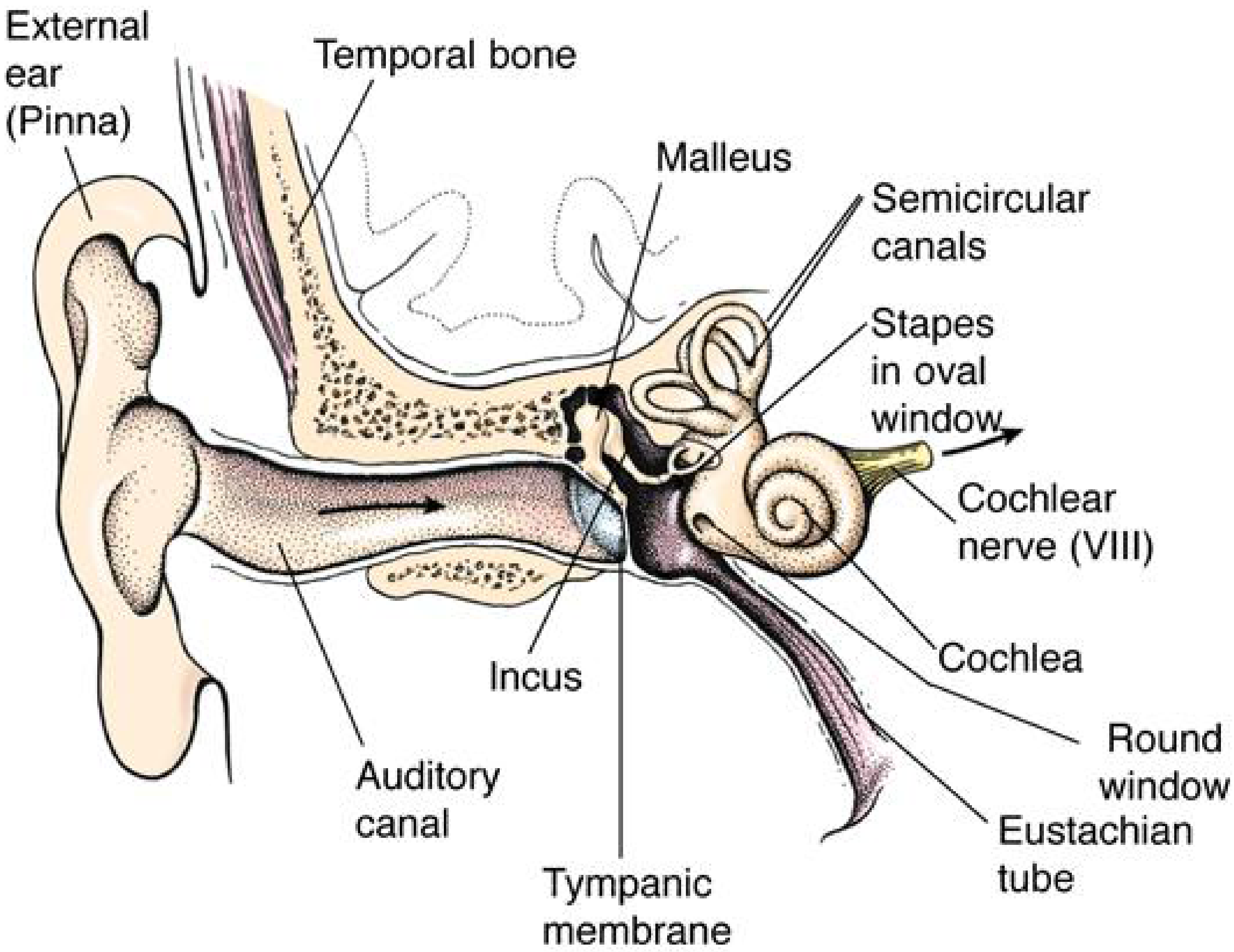
Fanto, M. et al. J Cell Sci 2004;117:527-533

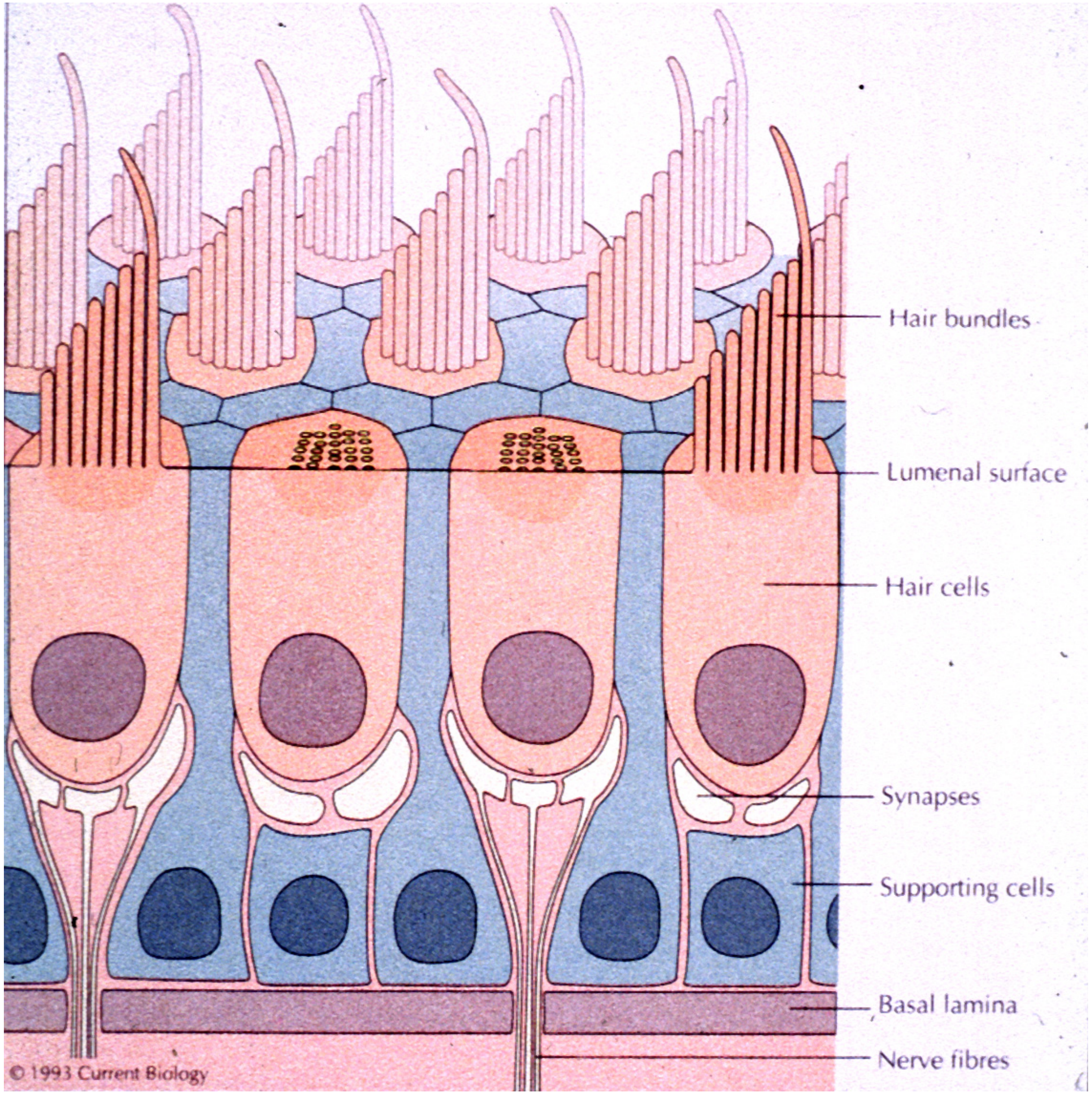
The asymmetric division of neuroblasts in the CNS depends on polarity in the apicobasal axis

In the PNS sensory organ precursors (SOPs) divide in the plane of the epithelium

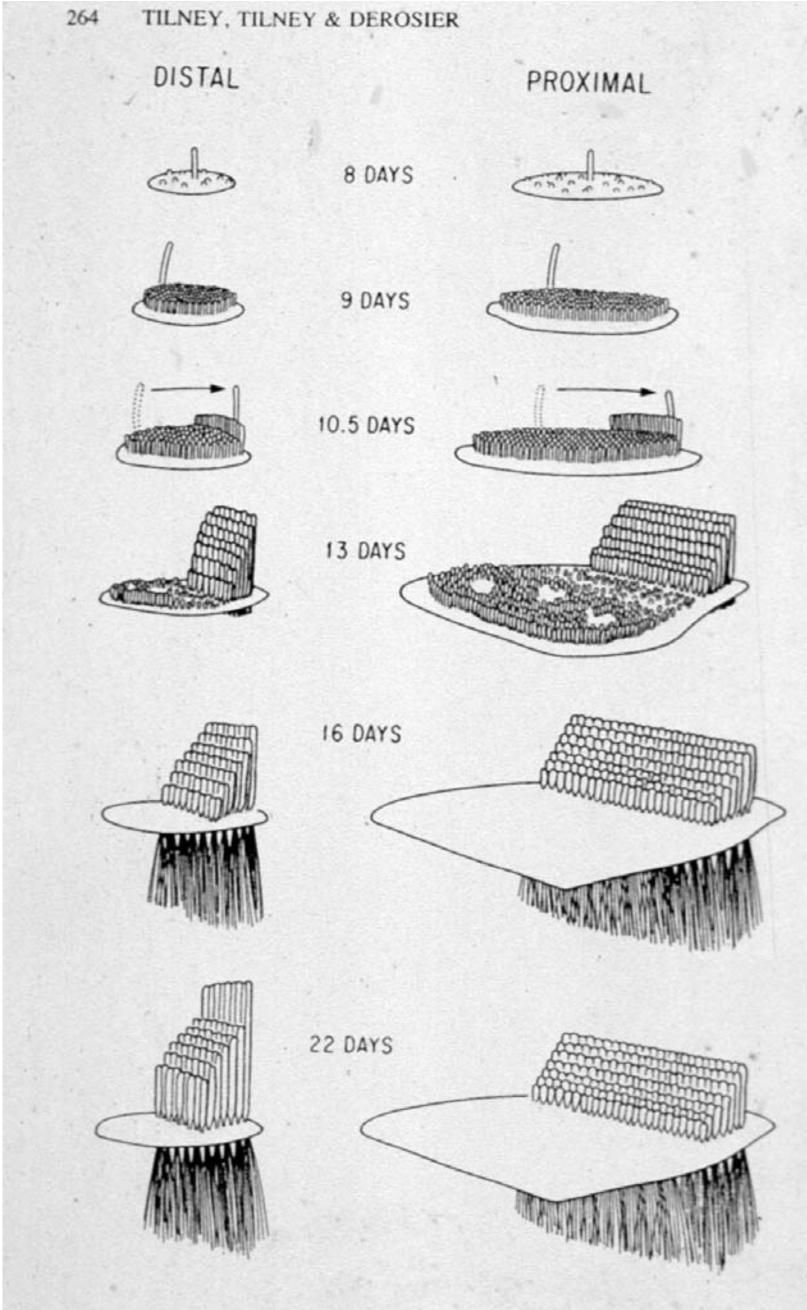
Now the Baz complex is <u>posterior</u> (rather than apical) and this localisation depends on Frizzled



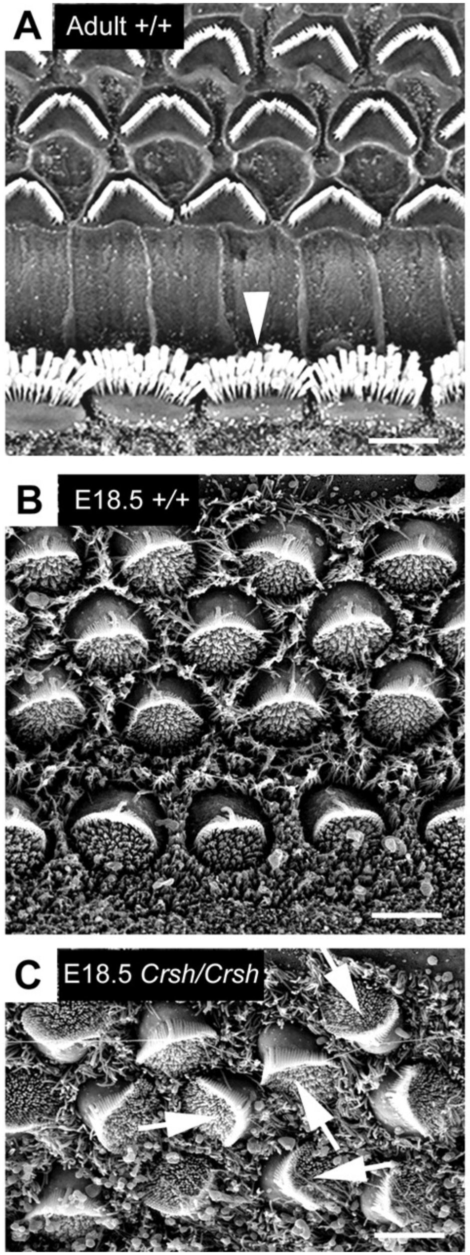

External ear (Pinna)
Temporal bone
Malleus
Semicircular canals
Stapes in oval window
Cochlear nerve (VIII)
Cochlea
Incus
Round window
Auditory canal
Eustachian tube
Tympanic membrane


Hair bundles
Lumenal surface
Hair cells
Synapses
Supporting cells
Basal lamina
Nerve fibres
© 1993 Current Biology

Development of hair cell stereocilia in the cochlea



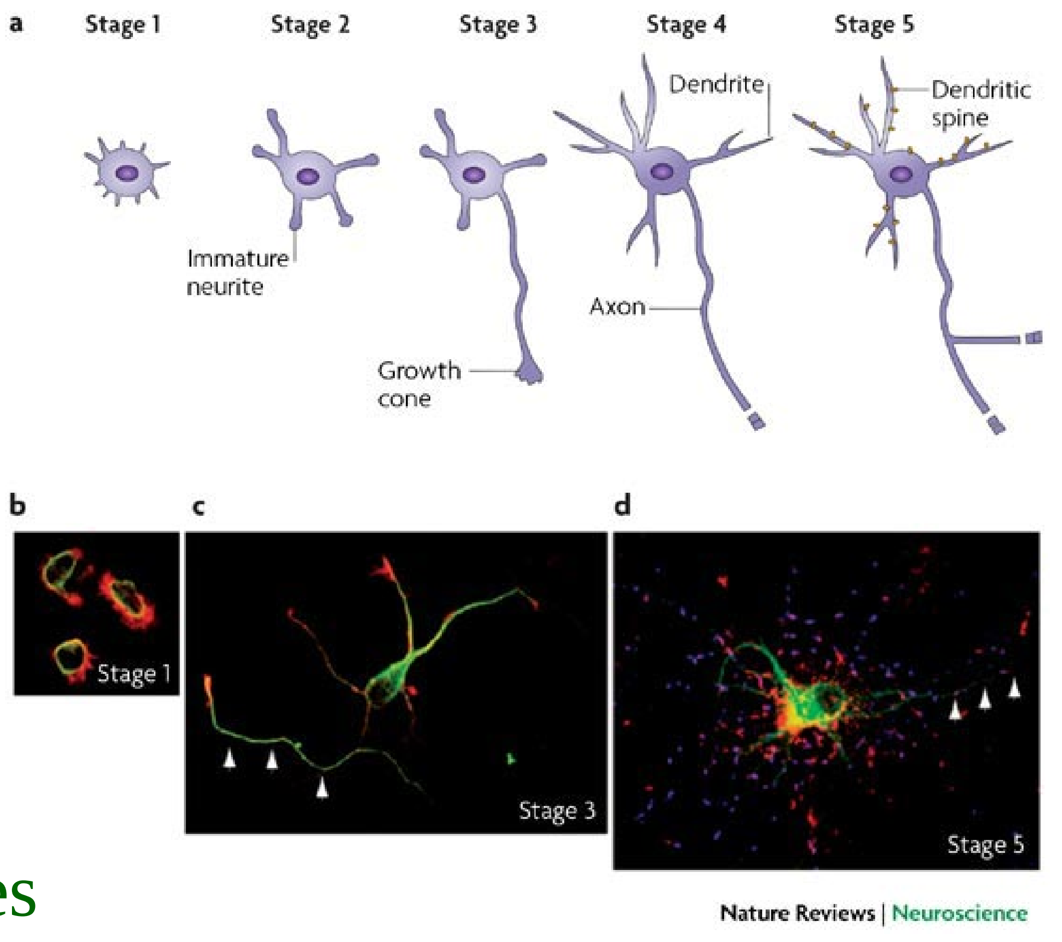
Mutations in PCP genes produce inner ear defects



SEM from wild type adult mouse

and wild type embryo

Iin an embryo mutant for Crash
(vertebrate homologue of *flamingo*)
the hair cell bundles are misaligned

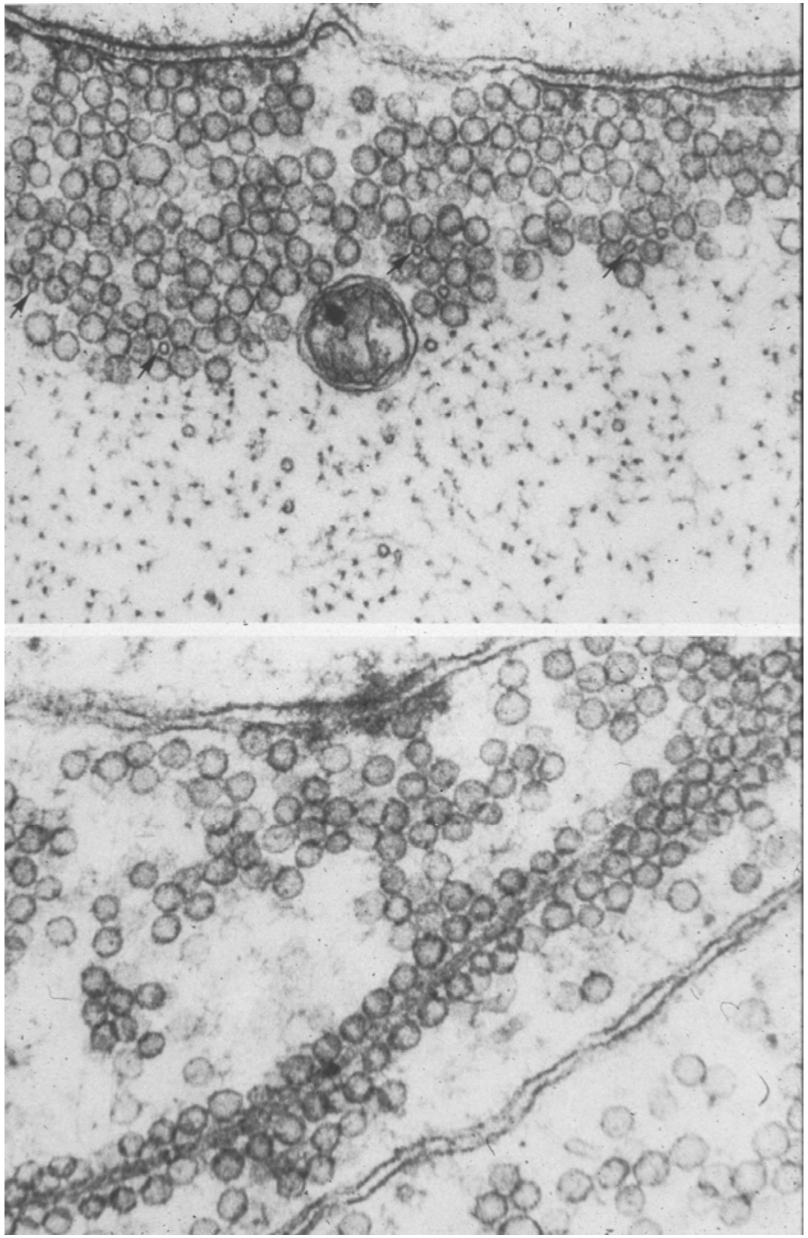


F-actin

Microtubules

Synapsin 1

Microtubules transport Membrane vesicles charged with cargo along axons



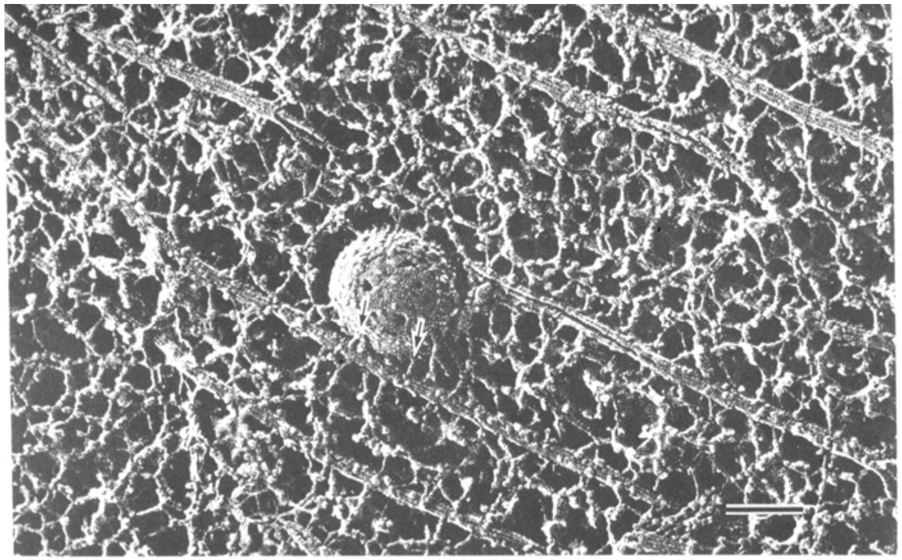
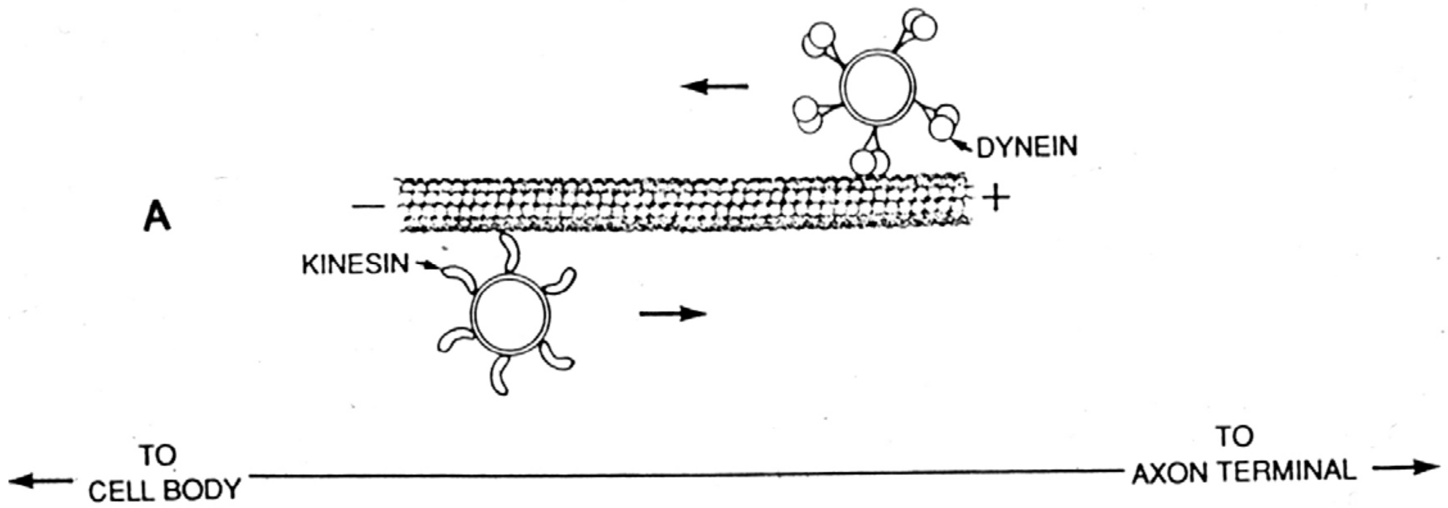
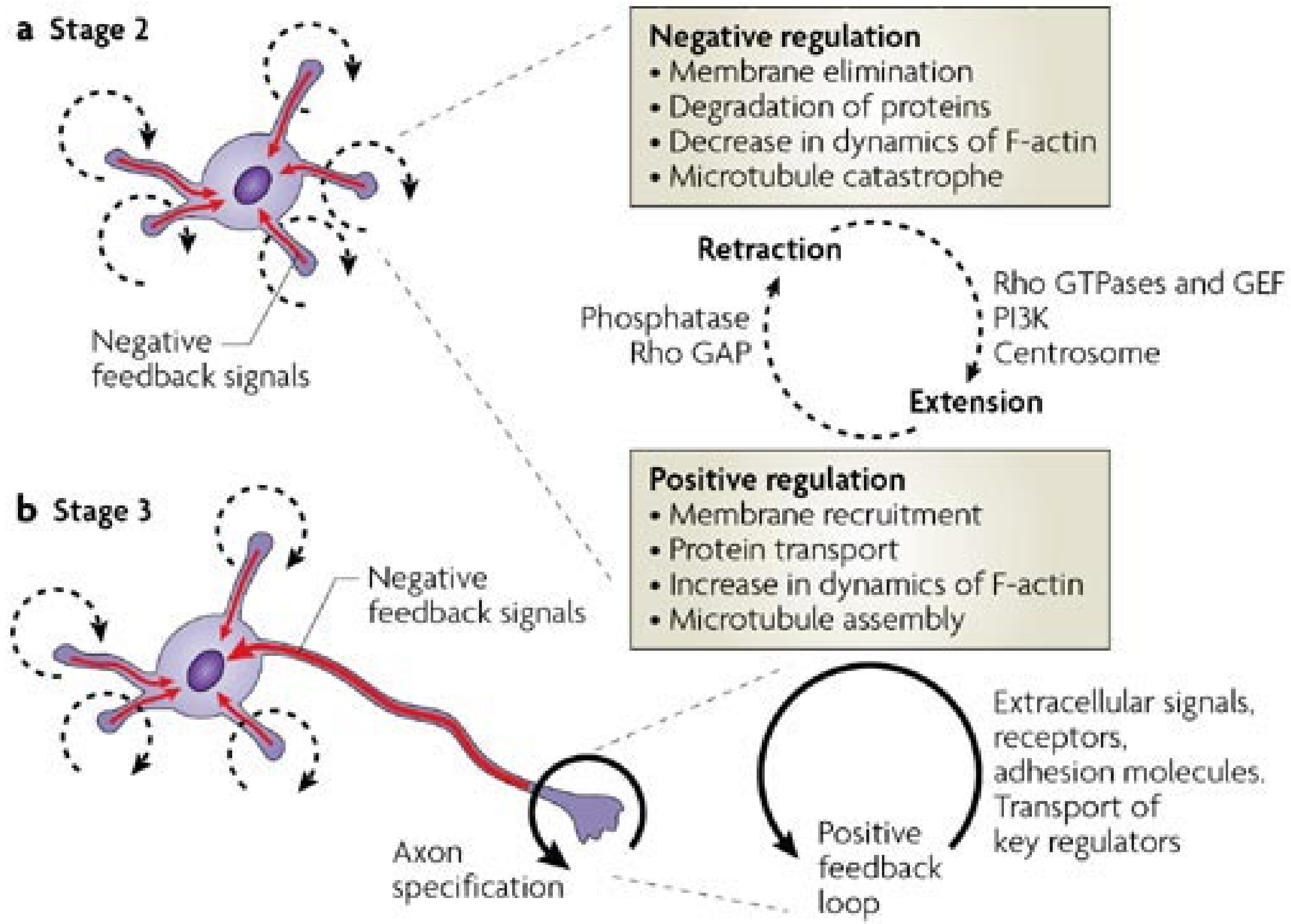


Fig. 1. A quick-frozen deep-etched crayfish axon permeabilized with saponin. An organelle is cross-linked with microtubule by fine strands (→). Bar, 0,1 µm. Published by permission (Hirokawa and Yorifuji, *Cell Motil* 1986, 6: 458–468)

Axonal transport depends on the activity of the microtubule motor proteins (dynein and kinesin)





Nature Reviews | Neuroscience

Genes, Development and the Emergence of Behaviour **ICTP Trieste 2010**

Cell polarity and neurogenesis Helen Skaer

We shall consider cell polarity in two axes: in the apicobasal (top-to-bottom) axis and in the planar (side-to-side) axis, focussing on the significance of cell polarity for the development of the nervous system.

Apicobasal polarity is pronounced in epithelial cells and it is here that many of the molecules and the processes that establish and maintain polarity have been uncovered. Three groups of proteins (the Crumbs, Bazooka and Scribbled complexes) interact with each other to establish apical and basolateral domains of the cell.

When neuroblasts (neural stem cells) delaminate from the ectodermal epithelium, the inheritance of this information is critically important in setting the fate of their progeny. At each division, one neuroblast daughter retains stem cell characteristics while the other, the ganglion mother cell (GMC), divides just once to produce differentiated neurons and/or glia. Apicobasal cell polarity regulates the asymmetric segregation of the determinants (such as Prospero, Brat and Numb), that set cell fates, and the orientation and position of cell division, which dictates daughter cell size.

As neurons begin to differentiate they form cell extensions or neurites. One of these neurites increases in length to become the axon. This growth is at the expense of other neurites, some of which persist as the much shorter dendrites. This process involves polarised trafficking of membrane and other materials along elements of the cell's internal architecture, the cytoskeleton. We shall discuss the evidence that the Bazooka complex, required to set up apicobasal polarity, might also act to establish neuronal polarity and the stabilisation of axons.

Planar polarity has also been studied in epithelia and the developing wing of the fly can be taken as a case study. It appears that two types of signalling act to establish planar polarity; long range interactions carried by graded signals and interactions between neighbouring cells carried by locally acting signals. This axis of polarity is essential for the development of the sensory nervous system in flies. The neural precursors (sensory organ precursors, SOPs) divide asymmetrically, as neuroblasts do, but they remain within the surface epithelium and depend on planar polarity cues to organise the segregation of determinants.

In another sensory system, the cochlea, planar polarity underlies the asymmetric organisation of individual hair cells and is also manifest in the graded changes in hair cell structure across the cochlear epithelium that allows us to hear tones of different pitch. There is increasing evidence that molecular elements of the planar polarity pathway described in the fly are also involved in setting this axis in the cochlea.

References
General background reading
Neural development.
Wolpert, L Principles of Development. OUP 2nd ed. Chapter 11
Mechanisms underlying cell fate determination
Wolpert (as above) pp15-25
Alberts et al Molecular Biology of the Cell Garland Press 4th ed. pp 1163-70
(the new 5th edition has this section on the DVD supplied with the book pp 1383-97)

Apico-basal polarity
Reviews:
Wodarz, A. 2002 Establishing cell polarity in development. Nature Cell Biology **4**: E39 – E44.
Nelson,W. J. 2003 Adaptation of core mechanisms to generate cell polarity. Nature **422**: 766-74.

Planar polarity
Review:
Zallen, J. A. 2007 Planar polarity and tissue morphogenesis Cell **129**: 1051 – 1063

Polarity in neurogenesis
Reviews:
Knoblich, J. 2008 Mechanisms of asymmetric stem cell division. Cell **132**: 583-59

Wodarz, A. and Huttner, W. 2003 Asymmetric cell division during neurogenesis in *Drosophila* and vertebrates. Mechanisms of Development **120**: 1297 – 1309

Arimura, N and Kaibuchi, K. 2007 Neuronal polarity: from extracellular signals to intracellular mechanisms. Nature Reviews Neuroscience **8**: 194- 205

Solecki, D. J. et al 2006 Neuronal polarity in CNS development. Genes and Development **20**: 2639-2647

And for planar cell polarity….if you are interested in cochlear hair cells
Frolenkov, G. et al 2004 Genetic insights into the morphogenesis of inner ear hair cells. Nature Rev. Genetics **5**: 489 – 498.

Papers for discussion
1. Choksi, S., Southall, A., Bossing, T., Edoff, K., de Wit, E., Fischer, B., van Steensel, B. & Brand, A. 2006 Prospero acts as a binary switch between self-renewal and differentiation in *Drosophila* neural stem cells. Dev. Cell **11**: 775-789

2. Isshiki, T., Pearson, B., Holbrook, S. and Doe, C. 2001 *Drosophila* neuroblasts sequentially express transcription factors which specify the temporal identity of their neuronal progeny. Cell **106**: 511-521.