

CHAPTER 11

- 1) Molecular signals, called morphogens, are able to diffuse over many cell diameters and establish concentration gradients, which confer positional information within their field of action. Cells at different positions in the field, exposed to different ambient morphogen concentration, turn on different transcription factors, establishing their positional value.
- 2) The same signal, in this case the diffusible morphogen FGF8, induces asymmetric responses in the anterior hindbrain and posterior midbrain because these two fields already express different transcription factors. This is known as a molecular pre-pattern. When the prepattern factor *Ir3*, normally expressed by the hindbrain, is misexpressed in the midbrain, this field responds to FGF8 by making cerebellum rather than optic tectum.
- 3) Local signaling centers form at tissue boundary regions, such as the floor plate or rhombomere boundaries, whose borders are positionally stabilized, sometimes by cell lineage-restriction, which helps them generate a consistent gradient. Local signaling centers are also known as secondary organizers because they are responsible for the progressive subdivision of the dorsoventral and anteroposterior axes of the neural plate, the whole of which is specified at an earlier stage by the primary (Spemann's) organizer at the dorsal blastopore lip of an amphibian embryo or the node of amniotes.
- 4) The hindbrain is subdivided by a series of transverse, cell-tight boundaries into a longitudinal set of segments (rhombomeres) that each make a different ultimate structure based on a shared developmental ground plan – variations on a theme. For the vertebrate neural tube, this pattern of true segmentation (merism) is unique to the hindbrain. Although similar in appearance to the segments of *Drosophila*, the hindbrain is segmented by different genes and morphogenetic mechanisms; segmentation is a developmental strategy that has evolved separately in arthropods and vertebrates.
- 5) Such an experiment would involve converting one rhombomere to take on the character of another in the series. Hox genes are thought to be crucial in conferring rhombomere identity. Misexpressing a Hox gene that is normally expressed in rhombomere 4 but not more anteriorly (e.g. *Hoxb1*) in rhombomere 2 induces the segment to form rhombomere 4-like cranial nerve patterns. Compare this with the *Drosophila* antennapedia mutant.
- 6) The floor plate at the midline of the neural plate is induced to express Shh by an Shh signal from the underlying notochord. Shh from the floor plate forms a spatial and temporal gradient in the ventral neural tube, with different transcription factors being either induced or repressed according to a cell's position on this gradient. A LIM homeodomain code underlies the variation of motor neuron subtype differentiation – for example, medial motor column vs lateral motor column.
- 7) Vertebrates can be thought of as upside-down insects. Although their central nervous systems later undergo distinct forms of morphogenesis, their neuroectoderm is initially patterned along AP and DV axes by conserved sets of homeobox genes – for example, the dorsal-to-ventral order of *msh*, *ind*, and *vnd* expression in the fly neuroectoderm is mirrored by the ventral-to-dorsal (lateral-to-medial in the flat neural plate of amniotes) expression of the homologous genes, *Msx*, *Gsh*, and *Nkx2.1*.
- 8) Lateral inhibition by the Delta-Notch pathway is crucial in nervous system development of both insects and vertebrates. This is a prominent example of cell-to-cell signalling that is mediated by direct cell contact. In the insect neuroectoderm, Delta-Notch signaling ensures the balanced formation of neurons and non-neurons in proneural clusters.
- 9) Both Numb and Pins are asymmetrically localised in both the neuroblast and the sensory organ precursor (SOP). In both cases Pins is required to orient the ensuing 'horizontal' cell division and in both cases Numb is inherited exclusively by daughter cell that forms neurons. However, whereas Pins is closely associated with Numb in the SOP, it moves to the opposite pole of the neuroblast, where on division it is inherited by the daughter cell that remains a neuroblast that continues to divide asymmetrically.
- 10) Radial glial cells develop directly from the columnar epithelium that constitutes the early neuroectoderm of vertebrates. They span the thickness of the neural tube with an endfoot on both ventricular and pial surfaces. One crucial function is to provide scaffolding along which newly formed neurons can migrate radially. Another is to divide to form neurons. Later in development, radial glial cells are a source of astrocytes.

- 11) In the spinal cord and other non-cortical CNS regions, newly born migrating neurons pile up beneath previously generated neurons forming the grey matter; their axons then form myelinated tracts (white matter) at the outer, pial surface. In the cortex, by contrast, new neurons pass through the older ones as they migrate radially and the axon tracts form on the inner, ventricular side of the grey matter. The inside-out configuration of cortical development allows evolutionarily unrestricted expansion of the grey matter, as it is not encased in the comparatively inextensible white matter.
- 12) Neurogenesis continues into the adult stage of mammals in certain key regions – particularly the olfactory bulb and the hippocampal dentate gyrus. Both these areas of the brain are equipped with pools of slowly dividing neural stem cells. The hippocampus is associated with learning and memory, seeming to involve new neuronal production as well synaptic plasticity. The hippocampus arises from the dorsal-most region of the telencephalic neuroectoderm.
- 13) The semaphorin family includes both secreted and membrane-bound members, most of which act to repel growth cones but, depending on the identity of the receptor and the target neuron's signal transduction machinery, some members can also attract. This target cell-dependent bifunctionality is also the case for the netrins, which are secreted, and the ephrins, which are membrane bound. Cadherins are membrane-bound attractors.
- 14) The two-dimensional array of retinal ganglion cells (RGCs) in the eye is maintained, with point-to-point precision, in the connections of their axons in the optic tectum, allowing a visual image to be faithfully and precisely projected onto the brain. Sperry's chemoaffinity hypothesis proposed that each RGC has a molecular label that enables it to connect with an appropriately labelled tectal neuron. The discovery of ephrin and Eph gradients in both the retina and the tectum now show that chemoaffinity actually involves a relatively small number of molecules to establish the necessarily precise positional matching.
- 15) In an amphibian, unlike a bird or mammal, CNS neurons regrow vigorously after their axons are cut. The regrowing optic nerve fibres in this experiment re-enter the tectum and find their original target cells, restoring vision. However, because the eye is upside down, so now is the visual image.
- 16) Neurotrophic factors, such as NGF, are required for neuronal survival. Neurotrophins are released by target cells during and following their innervation by afferents, but in limiting quantities. Only those afferents that receive neurotrophins through their receptors will survive; any excess afferents will die. This mechanism ensures size-matching between connected populations of neurons. When an additional limb bud is transplanted to the flank of a chick embryo, the resulting third leg is innervated by an enlarged lateral motor column containing motor neurons that normally would have died – the additional target has provided additional motor neuron survival factors.
- 17) Here, the space between pre- and post-synaptic neurons (the synaptic cleft) is all-important. Distinguish between a chemical synapse, at which a neurotransmitter is released and taken up, and an electrical synapse – where the membranes of the two cells are connected by gap junctions.
- 18) Muscle cells are coarsely prepatterned with respect to the distribution of neurotransmitter receptors (AChRs) on the central region of their surface. These become more tightly clustered in response to the Agrin signal from the motor neuron. Bidirectional signaling is followed by synapse formation. A muscle cell may initially be innervated by more than one motor neuron, but the synapses of all but the most powerful of the motor neurons are subsequently eliminated by competitive interaction.
- 19) In certain situations, such as in *C. elegans*, apoptosis is controlled intrinsically as a part of a genetic program – essentially a differentiation event to remove specific cells during development. More commonly, in vertebrates, neuronal death is controlled by factors external to the cell, such as the lack of required trophic factors.
- 20) Whereas the midbrain tectum is the principal target for retinal axons in anamniotes, this pathway is taken by a minor population of axons in amniotes – those concerned with light responses such as the pupillary reflex; retinal axons involved in image formation instead pass to the lateral geniculate nucleus (LGN) of the thalamus, and thence relayed to the visual cortex. In mammals that have binocular vision, the LGN on each side of the brain receives inputs from both eyes; these are initially intermixed but later segregate through neural activity into distinct layers. Projections from the LGN to the visual cortex are also intermixed and later segregate, again through neural competitive activity, into distinct left eye and right eye stripes – the ocular dominance columns. Information from the two eyes is subsequently integrated in higher areas of the visual cortex. Success in forming appropriate connections depends in large part on coincident neural activity between afferent and target neuron, which strengthens that synaptic coupling.