Neurite outgrowth and specificity

Brain development

Cerebral cortex, cerebellum, brain stem
motor cortex, somatosensory cortex
Visual system

Optic nerve growth from retinal ganglion to LGN

Choice points
Fasciculation
Optic chiasm
Target cells in LGN

Studies in invertebrate indicate:
Environmental cues are used.
Pathfinding axons (pioneer axons) and fasciculation
Guidepost cells ("Stepping stones")

FIGURE 3. Patterns of selective fasciculation of axons in the insect embryo. A fraction of the identified neurons in half of a segmental ganglion are labeled with their distinctive names, and the directions their axons take in the period of initial outgrowth are schematized. The axons form an orthogonal array of bundles by selective fasciculation. A given neuron, such as aCC (colored arrow, center), makes multiple choices as it grows, passing by some bundles (such as that formed by pCC, MP1, and dMP2) and joining up and growing along other bundles (such as that formed by U1, U2, RP1, and RP2). If the development of aCC is delayed so that its axon grows out at a later time, it apparently cannot read these environmental signals, and its growth cone wanders aimlessly in the northeast direction. Note that during neuronal development a given axon may grow along a certain bundle for part of its length, and then diverge and fasciculate with another bundle (see the path of RP1, upper left). Each of these distinctive fascicles are thought to express characteristic surface labels, some of which are illustrated in Figure 9. (From C. S. Goodman et al., 1984. Science 225: 1271–1279.)

FIGURE 4. Growth cones use many cues along their pathways. The direction of growth cone movements in the insect leg made by the sibling Ti1 neurons as they grow into the CNS indicates several of the cues they use to navigate. Growth cones always emerge in the proximal direction, toward the CNS. Other experiments suggest that this is due in part to a distal-proximal gradient of positional information in the appendage. The initial path of 50 μm, illustrated as segment a on the right, is then reoriented in a proximal-ventral direction as contact is made with the first guidepost cell, neuron Fe1. This forms segment b of the path. At this point, the growth cones orient toward the m1 and m2 cells, forming the c segment. The d segment is formed by a contact with the second guidepost cell, Tr1. From this point, the growth cones turn sharply to follow the segment boundary in the epithelium, forming part e of the pathway. The f segment is formed by a distinct reorientation towards the next guidepost cells, the Cx1 cells. Leaving these cells, the Ti1 growth cones follow a direct line into the CNS along the p cells. The swath that the growth cones sweep as the axons grow is illustrated by the colored region. (From M. Caudy and D. Bentley, 1986. J. Neurosci. 6: 1781–1795.)
Segmental innervation and motor pools

![Diagram showing dermatomes and cutaneous areas supplied by individual peripheral nerves]

FIGURE 5. Motor axon outgrowth patterns under altered conditions. The pathways taken by chick motor neurons projecting from segments T7 and LS1 were observed by local injections of HRP (color) into the spinal cord before (top) and after (bottom) the period of motor neuron death. In the experimental embryos, four segments of spinal cord were reversed (T7-L5) at an earlier stage. By stage 28, the injected axons had grown out to their appropriate muscle branches by taking novel routes through the axon plexus. (From C. Lance-Jones and L. Landmesser, 1980. J. Physiol. 302: 581-602.)

Stereotyped pathway (control)
Subsidiary mechanism (Experimental)
How do these growing axons interact and find the pathway?

Neuron-substrate interaction

1. Extracellular matrix (ECM)
   "Diverse set of axons can attach to ECM. collagen, fibronectin, laminin
   Laminin: adhesion domain (see Fig.6, pp. 396-397)
   neurite outgrowth domain
   heparansulfate proteoglycan binding"

2. Integrins (ECM receptors)
   "Heterodimer (α, β subunit: many)
   Binds to ECM
   Integration of extracellular signal into the cytoplasm
   Integrin interacts with cytoskeletal proteins
   Neuronal Adhesion molecules"

Cell-Cell interaction---important for fasciculation
   Cadherin (CAD) family
   Immunoglobulin superfamily
ECM-Integrin interaction and cytoskeleton

FIG. 1  Diagram illustrating the major structural proteins found in a focal adhesion of a cultured cell that is adhering to a glass coverslip coated with either fibronectin or vitronectin. Key to abbreviations: α-A, α-actinin; C, cysteine-rich protein; FN, fibronectin; Px, paxillin; PM, plasma membrane; TAL, talin; TEN, tensin; V, vinculin; VN, vitronectin; Z, zyxin. (Figure contributed by Dr. Susanne Bockholt, Dept. of Biology, Univ. of Utah.)
**CAD-CAD interaction**

- Homophilic, Ca\(^{2+}\) dependent interaction
  - Neural crest cell migration
  - Fasciculation
  - Other

**Neuronal CAD (N-CAD) CAD 6B, CAD 7**

During the emergence of neural crest cells from the neural tube, the expression of cadherins dynamically changes. In the chicken embryo, the early neural tube expresses two cadherins, N-cadherin and cadherin-6B (cad6B), in the dorsal-most region where neural crest cells are generated. The expression of these two cadherins is, however, down-regulated in the neural crest cells migrating from the neural tube; they instead begin expressing cadherin-7 (cad7).

Immunoglobulin family of cell adhesion molecules (CAMs)

Ca\(^{2+}\) independent homophilic/heterophilic interaction
One or more Ig domain
Transmembrane domain or GPI anchored

FIGURE 8. A schematic diagram of neural molecules that are members of the immunoglobulin superfamily. Many of these function as cell surface adhesion molecules. The immunoglobulin fold domains are indicated by the half circles, and fibronectin type III repeats are indicated by colored boxes. Thy-1, TAG-1, and variant forms of contactin and N-CAM are attached to the plasma membrane by a phosphoinositol linkage as indicated by arrows.
Cell Adhesion Molecules—promote neurite outgrowth

Thy-1: abundant in long axons, stabilizing neural membrane

$P_0$: abundant in peripheral myelin

N-CAM: spliced variants
- polysialic acid (PSA) embryonic form (glycosylation)
  PSA: developmental role
  endoneuraminidase $\rightarrow$ fasciculation $\uparrow$
  neuronal plasticity

L1: fasciculation
  along with N-CAM, L1 is indicated in neuronal plasticity