Section B and C

Volume-08

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5. DEVELOPMENTAL BIOLOGY

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A. BASIC CONCEPT OF DEVELOPMENT

Introduction:

Multicellular organisms do not spring forth fully formed. Rather, they arise by a relatively slow process of progressive change that we call **development.** In nearly all cases, the development of a multicellular organism begins with a single cell the fertilized egg, or **zygote**, which divides mitotically to produce all the cells of the body. The study of animal development has traditionally been called **embryology**, from that stage of an organism that exists between fertilization and birth. But development does not stop at birth, or even at adulthood. Most organisms never stop developing. Each day we replace more than a gram of skin cells (the older cells being sloughed off as we move), and our bone marrow sustains the development of millions of new red blood cells every minute of our lives. In addition, some animals can regenerate severed parts, and many species undergo metamorphosis (such as the transformation of a tadpole into a frog, or a caterpillar into a butterfly). Therefore, in recent years it has become customary to speak of **developmental biology** as the discipline that studies embryonic and other developmental processes.

A single cell, the fertilized egg, gives rise to hundreds of different cell types muscle cells, epidermal cells, neurons, lens cells, lymphocytes, blood cells, fat cells, and so on. This generation of cellular diversity is called **differentiation**. Our differentiated cells are not randomly distributed. Rather, they are organized into intricate tissues and organs. These organs are arranged in a given way: the fingers are always at the tips of our hands, never in the middle; the eyes are always in our heads, not in our toes or gut. This creation of ordered form is called **morphogenesis.** The sperm and egg are very specialized cells. Only they can transmit the instructions for making an organism from one generation to the next. The development of many organisms is influenced by cues from the environment. Certain butterflies, for instance, inherit the ability to produce different wing colors based on the temperature or the amount of daylight experienced by the caterpillar before it undergoes metamorphosis.

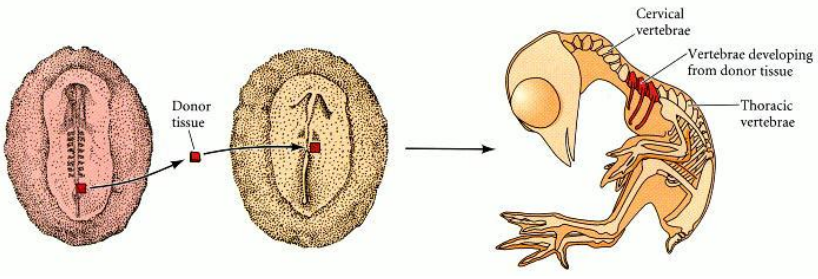
Potency:

The **developmental potential**, or potency, of a cell describes the range of different cell types it can become. The zygote and its very early descendents are totipotent - these cells have the potential to develop into a complete organism. Totipotency is common in plants, but is uncommon in animals after the 2-4 cell stage. As development proceeds, the developmental potential of individual cells decreases until their fate is determined. Driesch referred to the

embryo as an "harmonious equipotential system" because each of the composite cells had surrendered most of its potential in order to form part of a single complete organism. Each cell could have become a complete animal on its own. What made the cells cooperate instead of becoming autonomous entities? Recent evidence suggests that the "harmonious equipotential system" is the result of negative induction events that mutually restrict the fates of neighbouring cells. Jon Henry and colleagues in Rudolf Raff's laboratory (1989) showed that if one isolates pairs of cells from the animal cap of a 16-cell sea urchin embryo, those cells can give rise to both ectodermal and mesodermal components. However, their capacity to form mesoderm is severely restricted if they are aggregated with other animal cap pairs. Thus, the presence of neighbour cells, even of the same kind, restricts the potencies of both partners. Potency is also restricted when a cell is combined with its neighbours along the animal-vegetal axis.

Specification and commitment:

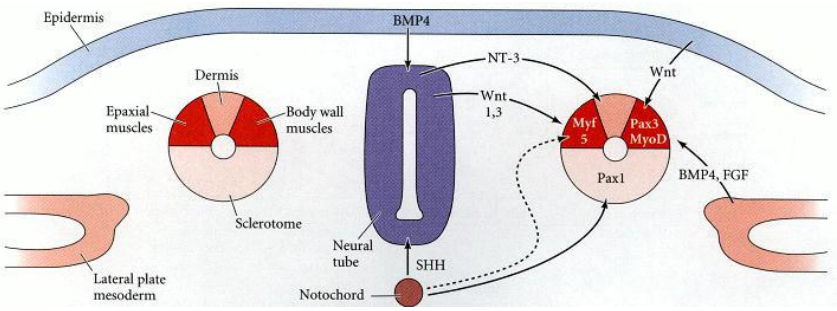
Axial specification: Although all the *somites* (blocks of cells) look identical, they will form different structures at different positions along the anterior-posterior axis. For instance, the ribs are derived from somites. The somites that form the cervical vertebrae of the neck and the lumbar vertebrae of the abdomen are not capable of forming ribs; ribs are generated only by the somites forming the thoracic vertebrae. Moreover, the specification of the thoracic vertebrae occurs very early in development. If one isolates the region of chick segmental plate that will give rise to a thoracic somite, and transplants this mesoderm into the cervical (neck) region of a younger embryo, the host embryo will develop ribs in its neck. Those ribs will form only on the side where the thoracic mesoderm has been transplanted (see Figure below), the somites are specified in this manner according to the *Hox* genes they express. Mice that are homozygous for a loss-of-function mutation of *Hoxc-8* will convert a lumbar vertebra into an extra ribbed thoracic vertebra.



Somites form (1) the cartilage of the vertebrae and ribs, (2) the muscles of the rib cage, limbs, and back, and (3) the dermis of the dorsal skin. Unlike the early commitment of the mesoderm along the anterior-posterior axis, the commitment of the cells within a somite to their respective fates occurs relatively late, after the somite has already formed. When the somite is

first separated from the presomitic mesoderm, any of its cells can become any of the somite-derived structures. However, as the somite matures, its various regions become committed to forming only certain cell types. The ventral medial cells of the somite (those cells located farthest from the back but closest to the neural tube) undergo mitosis, lose their round epithelial characteristics, and become mesenchymal cells again. The portion of the somite that gives rise to these cells is called the **sclerotome**, and these mesenchymal cells ultimately become the cartilage cells (chondrocytes) of the vertebrae and part (if not all) of each rib. Fate mapping with chick-quail chimeras has revealed that the remaining epithelial portion of the somite is arranged into three regions. The cells in the two lateral portions of the epithelium (those regions closest to and farthest from the neural tube) are muscle-forming cells. They divide to produce a lower layer of muscle precursor cells, the **myoblasts**. The resulting double-layered structure is called the **dermamyotome**, and the lower layer is called the **myotome**. Those myoblasts formed from the region closest to the neural tube form the **epaxial muscles** (the deep muscles of the back), while those myoblasts formed in the region farthest from the neural tube produce the **hypaxial muscles** of the body wall, limbs, and tongue. The central region of the dorsal layer of the dermamyotome is called the **dermatome**, and it generates the mesenchymal connective tissue of the back skin: the **dermis**. (The dermis of other areas of the body forms from other mesenchymal cells, not from the somites.) The dermamyotome may also produce the distal cartilage of the ribs, its lateral edge producing the most ventral portion of the rib.

Determination of the sclerotome and dermatome: The specification of the somite is accomplished by the interaction of several tissues. The ventral-medial portion of the somite is induced to become the sclerotome by paracrine factors, especially Sonic hedgehog, secreted from the notochord and the neural tube floor plate. If portions of the notochord (or another source of Sonic hedgehog) are transplanted next to other regions of the somite, those regions, too, will become sclerotome cells. Sclerotome cells express a new transcription factor, Pax1, that is required for their differentiation into cartilage and whose presence is necessary for the formation of the vertebrae. They also express I-mf, an inhibitor of the myogenic bHLH family of transcription factors that initiate muscle formation.



The dermatome differentiates in response to another factor secreted by the neural tube, neurotrophin 3 (NT-3). Antibodies that block the activities of NT-3 prevent the conversion of the epithelial dermatome into the loose dermal mesenchyme that migrates beneath the epidermis.

Determination of the myotome: In similar ways, the myotome is induced by at least two distinct signals. Studies involving transplantation and knockout mice indicate that the epaxial muscle cells coming from the medial portion of the somite are induced by factors from the neural tube, probably *Wnt1* and *Wnt3a* from the dorsal region and low levels of Sonic hedgehog from the ventral region. The hypaxial muscles coming from the lateral edge of the somite are probably induced by a combination of *Wnt* proteins from the epidermis and bone morphogenetic protein 4 (BMP4) from the lateral plate mesoderm. These factors cause the myotome cells to express particular transcription factors that activate the muscle-specific genes.

In addition to these positive signals, there are inhibitory signals that prevent a signal from affecting an inappropriate group of cells. For example, Sonic hedgehog not only activates sclerotome and myotome development; it also inhibits BMP4 signal from the lateral plate mesoderm from extending medially and ventrally (thus preventing the conversion of sclerotome into muscle). Similarly, Noggin is produced by the most medial portion of the dermamyotome and prevents BMP4 from giving these cells the migratory characteristics of hypaxial muscle. And what happens to the notochord, that central mesodermal structure? After it has provided the axial integrity of the early embryo and has induced the formation of the dorsal neural tube, most of it degenerates. Wherever the sclerotome cells have formed a vertebral body, the notochordal cells die. However, in between the vertebrae, the notochordal cells form the tissue of the intervertebral discs, the nuclei pulposi. These are the discs that "slip" in certain back injuries.

Specification and differentiation by the myogenic bHLH proteins: As we have seen, muscle cells come from two cell lineages in the somite. In both instances, paracrine factors instruct the myotome cells to become muscles by inducing them to synthesize the MyoD protein. In the lateral portion of the somite, which forms the hypaxial muscles, factors from the surrounding environment induce the Pax3 transcription factor. In the absence of other inhibitory transcription factors (such as those found in the sclerotome cells), Pax3 then activates the genes encoding two muscle-specific transcription factors, **Myf5** and **MyoD**. In the medial region of the somite, which forms the epaxial muscles, MyoD is induced through a slightly different pathway. MyoD and Myf5 belong to a family of transcription factors called the **myogenic bHLH** (basic helix-loop-helix) **proteins** (sometimes also referred to as the MyoD family).

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