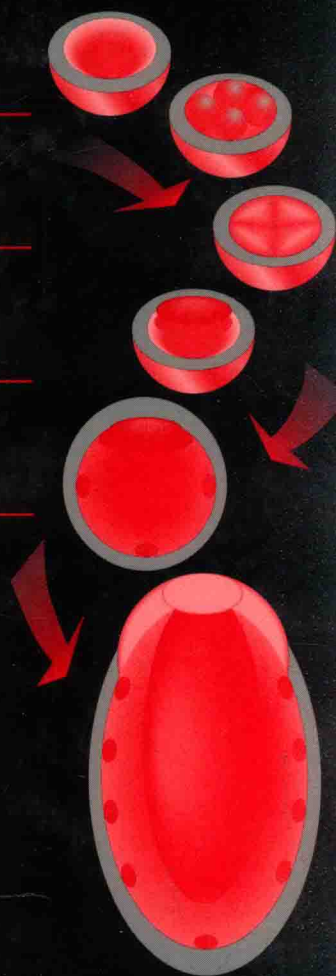


Hormones and Growth Factors in Development and Neoplasia

Edited by

Robert B. Dickson

David S. Salomon



HORMONES AND GROWTH FACTORS IN DEVELOPMENT AND NEOPLASIA

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ROBERT B. DICKSON
and
DAVID S. SALOMON



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**HORMONES AND
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PREFACE

FROM WORMS TO PEOPLE: THE EVOLUTION AND DEVOLUTION OF INTRACELLULAR COMMUNICATION

At the dawn of evolution of multicellular organisms, multiple independent body plans must have rapidly become established to fill the Precambrian seas (1). Unspecialized colonies of cells must have learned new ways of communicating with each other for improved survival and reproduction. Although we lack a window through time with which to view the biochemical and molecular bases of these critical processes, we can examine in great detail the mechanisms of cell–cell communication in the developmental and reproductive biologies of the simplest metazoans that are still extant. Although these simple organisms, such as represented by the worm *Caenorhabditis elegans*, have themselves been subject to continual selective pressures for the millions of years that separate them from humans, they provide remarkable insights into early versions of the same signaling pathways that form the bases of our own developmental and pathologic states.

C. elegans has provided a bonanza of clues to the evolution of cell–cell communication. The development of a hermaphrodite vulva in this tiny worm is initiated when a primitive gonadal cell expresses LIN-3, an ancient growth factor-like molecule. LIN-3 triggers division and differentiation in nearby vulval precursor cells. *C. elegans* is such an elegant system for these types of studies because it is so small that the fate of each of its cells is known throughout development. In addition, the study of its genetic material is very advanced and investigators can establish, by gene addition or knockout techniques, the relative importance of individual developmental signals, their cellular receptors, and their intracellular signaling molecules. Although the evolutionary origins of *C. elegans* are shrouded in the Cambrian era, LIN-3 is strikingly similar to a well-known growth factor family (epidermal growth factor,

EGF) of considerable importance to mammalian development and cancer. LIN-3 acts through a receptor termed let-23 and a signal transduction pathway involving tyrosine phosphorylation, the Ras protein, and a mitogen-activated protein (MAP) kinase molecule; again, each is strikingly similar to its mammalian counterparts. *C. elegans* thus provides us with a profound informative system for dissection of the roles of signaling molecules in development, particularly of reproductive structures.

Reproductive tissues became the focus of this book for several reasons. First, due to the importance of these structures for the propagation of the species, they have become complex in their development, involving interaction of multiple extracellular influences. Second, at least some component of the development of reproductive structures occurs postnatally. In many cases, periodic tissue growth, differentiation, and death characterize reproductive cycles. Third, and of particular concern to human society today, cancers of the reproductive tissues (breast, prostate, uterus, cervix, ovaries, testes) are extraordinarily prevalent. Thus, as we move from relatively simple developmental signaling in the reproductive system of a small worm to greater and greater complexity and greater longevity through evolution, there may be greater opportunities for signaling-associated pathologies. Reproductive cancers may be particularly important in this respect (2,3).

With the evolution of arthropods, cell-cell signaling becomes more complex than in *C. elegans*, with the need to orchestrate more different cell types through more stages and with the onset of sexual reproduction. Here our model system is *Drosophila*, the common fruit fly. Growth factor families have now expanded to encompass more members, receptors are now interactive receptor families with multiple intracellular signal transduction pathways, and certain growth factors counter the effects of other factors to finely tune developmental and homeostatic processes. Of critical importance in the overall schema of arthropod development is the need to orchestrate the behavior of distant tissues by neural, neuroendocrine, and endocrine mechanisms. A key family of endocrine effectors, the steroid hormones, typified by ecdysone, are now produced by lipid metabolic processes. This family, as we will see, plays an ever-increasing role in vertebrates (4,5).

We have several important model systems with which to study early vertebrate evolution. Lowest on the evolutionary tree is *Amphioxus*, a tiny fish with a notochord rather than a long vertebrate. A very important fish model also available to researchers is the Zebrafish. We have chosen an amphibian representative, *Xenopus*, the common frog, as a model system to highlight. Our interest here is in the development of the complex egg. Steroid hormones have now evolved to the forms important in our own reproduction: estrogens, progestins, and androgens (6).

Next, we move to the development of mammals. The common house mouse, *Mus musculus*, is the most well established model system here. The mouse has been well studied with respect to its genes, chromosomes, embryogenesis, later development, and reproductive biology. The ability of biologists to selectively inactivate or activate expression of genes in this model with tissue- and development-dependent specificity has led to remarkable insights into human development and pathology. In the reproductive tissues of the mouse, incredible complexity of interaction has developed between hormones and growth factors (2,6).

As we sequentially examine cell–cell communication from both local and systemic perspectives, it becomes clear that the two types of communication have co-evolved, each interacting with the other. This interdependence of local and systemic signaling is particularly evident in the male and female reproductive tracts and in the female accessory tissue—the mammary glands. Each of these tissues requires a highly orchestrated endocrine environment in order to coordinate and control local cell–cell and tissue–tissue interactions. Each of these tissues is designed to undergo growth during sexual maturation (puberty) and cycles of growth (male reproductive tissues) or growth and death (female primary and accessory tissues) (6–8).

It is within the complex regulation of postnatal cellular proliferation and death in these male and female reproductive tissues that human cancer most often arises and most often leads to death (with only the important exception of cigarette smoking-induced lung cancer). One in eight women in the United States will contract breast cancer in her lifetime, and one in five men will contract prostate cancer. The costs of this epidemic in human suffering, economic hardship, legal deliberations, and regulatory paralysis are incalculable. It may be that this state of affairs is the result of an unfortunate interaction of greater longevity, gradual accumulation of autonomous or environmentally induced genetic defects, and a tendency for such complex regulatory systems to move toward chaos and disease (3,9,10).

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PART I

GROWTH FACTORS AND STEROID HORMONES IN THE DEVELOPMENT OF INVERTEBRATES AND AMPHIBIANS

