

Chapter 1 : Developmental and Cellular Skeletal Biology - Europe PMC Article - Europe PMC

Developmental and Cellular Skeletal Biology reviews the development, growth, and cell biology of the skeleton. The monograph provides a comprehensive overview of the aspects of skeletal biology, focusing mainly on the cellular level.

Sinauer Associates ; The Development of Muscle 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 Maroto et al. 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. The proteins of this family all bind to similar sites on the DNA and activate muscle-specific genes. For instance, the MyoD protein appears to directly activate the muscle-specific creatine phosphokinase gene by binding to the DNA immediately upstream from it Lassar et al. MyoD also directly activates its own gene. Therefore, once the myoD gene is activated, its protein product binds to the DNA immediately upstream of the myoD gene and keeps this gene active. While Pax3 is found in several other cell types, the myogenic bHLH proteins are specific for muscle cells. Transfection of genes encoding any of these myogenic proteins into a wide range of cultured cells converts those cells into muscles Thayer et al. Since the MyoD protein and its relatives are so powerful that they can turn nearly any cell into a muscle cell, the synthesis of this protein has to be inhibited at numerous steps. Numerous inhibitors of MyoD family gene expression and protein function have been found. Experiments with chimeric mice and cultured myoblasts showed conclusively that these cells align together and fuse to form the multinucleated myotubes characteristic of muscle tissue. Thus, the multinucleated myotube cells are the product of several myoblasts joining together and dissolving the cell membranes between themselves Konigsberg ; Mintz and Baker Muscle cell fusion begins when the myoblasts leave the cell cycle. As long as particular growth factors particularly fibroblast growth factors are present, the myoblasts will proliferate without differentiating. If this adhesion is experimentally blocked, no further muscle development ensues, so it appears that the signal from the integrin-fibronectin attachment is critical for instructing the myoblasts to differentiate into muscle cells Figure A Determination of myotome cells by paracrine factors. B Committed myoblasts divide in the presence of growth factors primarily FGFs , but show no obvious muscle-specific proteins. C-D When the growth more The second step is the alignment of the myoblasts together into chains. This step is mediated by cell membrane glycoproteins, including several cadherins and CAMs Knudsen Recognition and alignment between cells takes place only if the two cells are myoblasts. Fusion can occur even between chick and rat myoblasts in culture Yaffe and Feldman ; the identity of the species is not critical. The third step is the cell fusion event itself. As in most membrane fusions, calcium ions are critical, and fusion can be activated by calcium ionophores, such as A, that carry calcium ions across cell membranes Shainberg et al. Fusion appears to be mediated by a set of metalloproteinases called meltrins. These proteins were discovered during a search for myoblast proteins that would be homologous to fertilin, a protein implicated in sperm-egg membrane fusion. Multinucleated myotubes could arise either as 1 a fusion event between several mononuclear myoblasts, or 2 as a string of mitoses within a single myoblast. The former is thought to be the mechanism for myotube formation in skeletal muscle; the latter is thought to be the way heart myotubes are formed.

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Research topics in cellular and developmental biology include structure and dynamics of the cell cytoskeleton, molecular motors, chemical biology, the nuclear envelope, lncRNAs, regeneration, developmental biomechanics, vertebral column development, neural and epidermal stem cells, and systems developmental biology. Research in neurobiology focuses on growth cone motility, neural differentiation, synaptogenesis, visual perception, olfaction, and the formation of topographic maps. A Special Program in Plant Sciences provides research and training in the molecular genetics of flowering, epigenetics, the physiology of hormone action, pathogen defense systems, sex determination, and the circadian clock. Because of the breadth of the department, students are provided with unique training and research opportunities for interdisciplinary studies. To enter the Ph. Special Admissions Requirements Applicants should have obtained training in the structure, development, and physiology of organisms; the structure, biochemistry, and physiology of cells; genetics; elementary calculus; elementary physics; inorganic and organic chemistry; statistics or advanced mathematics. Lack of some prerequisites can be made up in the first year of graduate study. Students having different science training, such as degrees in chemistry, physics, or engineering, are encouraged to apply. Special Requirements for the Ph. With the help of a faculty committee, each student will plan a specific program that includes appropriate courses, seminars, laboratory rotations, and independent reading fitted to individual needs and career goals. There is no foreign language requirement. At the beginning of the third term of study, the student meets with a faculty committee to decide on a preliminary topic for dissertation work and to define the research areas in which the student is expected to demonstrate competence. By the end of the fall term of the second year, each student prepares a dissertation prospectus outlining the research proposed for the Ph. The student is admitted to candidacy for the Ph. The student should complete the requirements for admission to candidacy by the end of the fall term of the second year and no later than the end of the second year of study. Following admission to candidacy, students are required to meet with their thesis advisory committee at least once a year. The remaining requirements include completion of the dissertation research, presentation and defense of the dissertation, and submission of acceptable copies of the dissertation to the Graduate School and to the Center for Science and Social Science Information CSSSI. All students are required to teach in two one-term TF level 10 courses during their Ph. Scientific Integrity in Biomedical Research, to fulfill the responsible conduct and ethics in research requirement. This requirement must be met prior to registering for a second year of study. The minimum requirements for award of the Master of Science degree are 1 two academic years registered and in residence full-time in the graduate program; 2 satisfactory completion of the first two years of study and research leading to the Ph. No courses that were taken prior to matriculation in the graduate program, or in Yale College, or in summer programs may be applied toward these requirements. Prospective applicants are encouraged to visit the BBS website <https://www.bbs.yale.edu/>. Attendance is taken, and students who attend both sessions receive a grade of Satisfactory. Cellular and molecular mechanisms of immune recognition. Effector responses against pathogens. Immunologic memory and vaccines. Basic concepts in cell and membrane physiology are synthesized through exploring the function of skeletal, smooth, and cardiac muscle. The physical basis of blood flow, mechanisms of vascular exchange, cardiac performance, and regulation of overall circulatory function are discussed. Respiratory physiology explores the mechanics of ventilation, gas diffusion, and acid-base balance. Renal physiology examines the formation and composition of urine and the regulation of electrolyte, fluid, and acid-base balance. Organs of the digestive system are discussed from the perspective of substrate metabolism and energy balance. Hormonal regulation is applied to metabolic control and to calcium, water, and electrolyte balance. The biology of nerve cells is addressed with emphasis on synaptic transmission and simple neuronal circuits within the central nervous system. The special senses are considered in the framework of sensory transduction. Weekly discussion sections provide a forum

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for in-depth exploration of topics. Graduate students evaluate research findings through literature review and weekly meetings with the instructor. Molecular Machines in Human Disease Emile Boulpaep The course focuses on understanding the processes that transfer molecules across membranes at the cellular, molecular, biophysical, and physiological levels. Students learn about the different classes of molecular machines that mediate membrane transport, generate electrical currents, or perform mechanical displacement. Emphasis is placed on the relationship between the molecular structures of membrane proteins and their individual functions. The interactions among transport proteins in determining the physiological behaviors of cells and tissues are also stressed. Molecular motors are introduced and their mechanical relationship to cell function is explored. Students read papers from the scientific literature that establish the connections between mutations in genes encoding membrane proteins and a wide variety of human genetic diseases. Review of basic biochemical concepts including chemical reactions, ligand binding to receptors, cooperativity, and Michaelis-Menten enzyme kinetics. Deep exploration of biological systems including: Students learn to model using MATLAB in a series of in-class hackathons that illustrate biological examples discussed in lectures. How do cells compute, how do they count and tell time, how do they oscillate and generate spatial patterns? Topics include time-dependent dynamics in regulatory, signal-transduction, and neuronal networks; fluctuations, growth, and form; mechanics of cell shape and motion; spatially heterogeneous processes; diffusion. This year, the course spends roughly half its time on mechanical systems at the cellular and tissue level, and half on models of neurons and neural systems in computational neuroscience. Topics include the most recent tools and strategies used by government agencies, industrial labs, and academic research to adapt biological and chemical compounds as medical treatments, as industrial agents, or for the further study of biological systems. Candidates Douglas Kankel A two-credit course taken in the third-to-last term typically the second term of the junior year. At the end of this course, students complete a detailed prospectus describing their thesis project and the work completed thus far. The committee evaluates an oral and written presentation of this prospectus; the evaluation determines whether the student may continue in the combined program. Required of students in the joint B. The modules cover a broad range of PEB research areas and skills. The course starts with an introduction to Matlab, since Matlab is used throughout the course for analysis, simulations, and modeling. During this course, students give an oral presentation describing their work. At the end of the course, students are expected to present their work to the department in the form of a poster presentation. In addition, students are expected to give an oral thesis defense, followed by a comprehensive examination of the thesis conducted by the thesis committee. Upon successful completion of this examination, as well as other requirements, the student is awarded the combined B. Emphasizes fundamental issues of cellular organization, regulation, biogenesis, and function at the molecular level. Students who have not taken courses in these areas can prepare by reading relevant sections in basic molecular cell biology texts. We recommend Pollard et al. The class is devoted to the reading and critical evaluation of classical and current papers. Students also read a small selection of primary papers illustrating the very best of genetic analysis and dissect them in detail in the discussion sections. While other Yale graduate molecular genetics courses emphasize molecular biology, this course focuses on the concepts and logic underlying modern genetic analysis. The course considers the basic physical chemistry required in cellular and molecular biology but does not require a previous course in physical chemistry. One class per week is a lecture introducing a topic. The second class is a discussion of one or two research papers utilizing those methods. Does not count for graduate course credit for BQBS graduate students. Detailed critique of papers from primary literature and discussion of novel technologies, with specific attention to the role of epigenetics in development and its impact on human health. Students read assigned papers in advance. Discussion focuses on experimental design used by the authors, results of the experiments, and conclusions drawn by the authors. The use of evolutionarily conserved signaling pathways to carry out developmental decisions in a range of animals is highlighted. Course work includes student participation in critical analysis of primary literature and a research proposal term paper. Mining and Modeling Mark Gerstein Biomedical data science encompasses

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the analysis of gene sequences, macromolecular structures, and functional genomics data on a large scale. It represents a major practical application for modern techniques in data mining and simulation. Specific topics to be covered include sequence alignment, large-scale processing, next-generation sequencing data, comparative genomics, phylogenetics, biological database design, geometric analysis of protein structure, molecular-dynamics simulation, biological networks, normalization of microarray data, mining of functional genomics data sets, and machine-learning approaches to data integration. Two students each give thirty-minute presentations in each class session. Students are required to present every year beginning in their third year in the MCDB program. Each MCDB graduate student is expected to attend at least 80 percent of the class sessions. Two faculty members co-direct the course, attend the seminars, and provide feedback to the students.

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