

October 18, 2007

CLOCK GENES, CELL AUTONOMY AND CIRCADIAN ORGANIZATION IN MAMMALS

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Circadian rhythms represent an evolutionarily conserved adaptation to the environment that can be traced back to the earliest life forms. In animals circadian behavior can be analyzed as an integrated system - beginning with genes leading ultimately to behavioral outputs. In the last decade, the molecular mechanism of circadian clocks has been uncovered by the use of phenotype-driven (forward) genetic analysis in a number of model systems. The discovery of 'clock genes' also led to the realization that the capacity for circadian gene expression is widespread throughout the body in mammals. The cellular autonomy of circadian clocks has raised a number of questions concerning synchronization and coherence of rhythms at the cellular level as well as circadian organization at the systems level. I will discuss recent work that addresses these issues and that examines a number of levels of complexity within the circadian system.

November 15, 2007

MODELING CANCER AND CANCER GENOMES

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This year marks the centennial of the mouse in cancer science. Engineered mouse models have been instrumental in illuminating key molecular, genomic and physiological factors that conspire to drive the development of cancer, and maintain the malignant state. We have explored the intimate association between the aging process and cancer, and how common adult cancers acquire rampant chromosomal aberrations. A confluence of telomere dysfunction, impaired DNA damage signaling, and age- or disease- accelerated epithelial renewal play critical roles in creating genomic events needed to drive the malignant process. We have also defined the extent to which telomeres influence the normal aging process and lifespan and contribute to stem cell and tissue homeostasis. These studies have provided insights into the pathogenesis of inherited and acquired degenerative diseases, among leading causes of death worldwide. Lastly, we have proven the utility of the mouse in comparative oncogenomics and proteomics in facilitating the identification of cancer genes and early detection biomarkers.

January 17, 2008

LIMB DEVELOPMENT: EMBRYOLOGY AND GENETICS TO EVO-DEVO

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The embryonic vertebrate limb is a classic paradigm for the study of pattern formation, cell growth and death, and skeletal formation. Our understanding of the molecular signals that regulate limb patterning is relatively complete. However, many questions remain as to how these signals are interpreted and translated into skeletal elements that are adapted to the needs of each animal on land, sea and air. Outstanding questions in patterning and skeletal formation include how and when are limb cells specified and acquire distinct cell fates in order to contribute to specific skeletal elements and what are the cellular and molecular mechanisms that lead to the establishment of the skeletal elements of the correct size and shape? Our work has contributed to answers to these questions. Moreover, our experiments have shown that our current knowledge is deep enough to begin to unravel the molecular mechanisms that underlie evolutionary change in other animals such as the bat.

February 21, 2008

STEM CELL REGULATION IN VIVO WITHIN TISSUE NICHES

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Adult stem cells mediate tissue repair and replenishment within organisms spanning a broad phylogenetic range from Planaria to humans. Drosophila genetic technology allows these rare cells to be identified and analyzed with single-cell and single-gene resolution. Marking tissue stem cells and their immature (transit-amplifying) progeny using inducible lineage tracers reveals that both germline and somatic gonadal stem cells are maintained within distinct tissue niches. Niche-bound stem cells compete with the daughters of other stem cells for continued niche occupancy, a process that may mitigate the effects of somatic mutations. Other stem cells, such as multipotent intestinal stem cells, program their daughters to become enterocytes or enteroendocrine cells by sending a strong or weak Notch signal, respectively. How stem cells remain undifferentiated within the niche, and how their daughters initiate differentiation and revert back to the stem cell state under appropriate conditions remain central questions. The ubiquitin-specific protease Scrawny appears to play a common role, as it is needed to maintain at least four different types of stem cell. Scrawny contributes to gene silencing in vivo and recombinant Scrawny deubiquitylates Histone H2B in vitro, suggesting a prominent role for chromatin-mediated gene repression.

March 20, 2008

THE MICROENVIRONMENT/GENOME AXIS IN TISSUE SPECIFICITY: THE ROLE OF EXTRACELLULAR MATRIX AND ORGAN ARCHITECTURE

Mina J. Bissell, Ph.D.

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How tissue specificity is maintained and why it is essentially lost in cancer are outstanding questions in biology. In the mammary gland, it is clear that both the architecture of the gland and its ability to synthesize and transport milk proteins are dependent on tissue polarity and maintenance of an intact and functional basement membrane. We have developed robust 3-D assays that mimic the morphology and function of the epithelial cells within the gland. We show that laminin 111 signals via $\alpha 1$ integrin to alter polarity, cytostructure and chromatin structure and the status of STAT5 phosphorylation and other transcription factors to allow milk production.

In malignant cells we show that restoring unit breast structure (the acinus) by reducing signaling through $\alpha 1$ integrin restores "normal" phenotype in 3-D cultures reversibly and prevents tumor formation. New model systems using branching morphogenesis in normal gland clarify the supreme importance of tissue architecture in morphogenesis and are shedding light on how cancer cells could usurp the normal pathways to invade and metastasize.

April 17, 2008

RNAI FROM MECHANISM TO MEDICINE

Craig C. Mello, PhD

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While investigating the genetic workings of the microscopic worm, *C. elegans*, Mello and colleague Andrew Fire, PhD, of the Carnegie Institution of Washington, discovered RNAi, a natural but previously unrecognized process by which a certain form of RNA can be manipulated to silence—or interfere with—the expression of a selected gene. The discovery, published in the journal *Nature* in 1998, has had two extraordinary impacts on biological science. One is as a research tool: RNAi is now the state-of-the-art method by which scientists can knock out the expression of specific genes in cells, to thus define the biological functions of those genes. But just as important has been the finding that RNA interference is a normal process of genetic regulation that takes place during development. Thus, RNAi has provided not only a powerful research tool for experimentally knocking out the expression of specific genes, but has opened a completely new and totally unanticipated window on developmental gene regulation. RNAi is now showing promising in the clinic as a new class of gene-specific therapeutics.

May 15, 2008

THE HUMAN MICROBIOME PROJECT: EXPLORING THE MICROBIAL SIDE OF OURSELVES

Jeffrey I. Gordon, MD

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Our genetic landscape is a summation of the genes embedded in our human genome and the genomes of our microbial partners (the microbiome). Our metabolic features are an amalgamation of human and microbial traits. Therefore, understanding of the range of human genetic and physiologic diversity means that we must characterize our microbiome, as well as the factors that influence the assembly, stability, functions and variations in our microbiota. The results should provide an additional perspective about contemporary human biology, as we assess how our lifestyles, cultural and societal norms, socioeconomic status, and changing biosphere are influencing our 'micro'-evolution, and thus our health. Therefore, members of my lab are exploring the following questions: What are the genomic and metabolic foundations of our mutually beneficial relationships with gut microbes? How do we acquire our microbiota? How stable is it? Do humans share an identifiable core 'microbiome'? How do variations in the microbiome correlate with and contribute to health and disease? How can we manipulate our gut microbial communities to optimize their performance in the context of an individual, or a population?

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