Motamedi Laboratory

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Multi-cellular organisms possess a variety of tissues composed of cell types, which perform a multitude of functions necessary for life. Interestingly, all cells within an individual share the identical set of genes. So how do cells acquire different identities and functions? During development, cells establish unique identities by altering their gene expression patterns – turning on or off certain genes. Epigenetics is a molecular memory system by which a cell ensures that the same gene expression pattern is inherited at division thus establishing stable cell lineages throughout development. In cancers, cells lose their ability to retain their correct identity and display aberrant gene expression patterns. Epigenetic aberrations occur at all stages of malignancies, from tumor formation to metastasis. The Motamedi laboratory uses the fission yeast to model epigenetics in an effort to understand the precise molecular mechanisms involved in regulating this process. This work has led to several novel discoveries which may be used as novel targets for treating cancers.

Epigenetic changes are stable and heritable alterations to gene expression patterns without concomitant mutations in the responsible genes. Disruption to epigenetic regulation leads to aberrant gene expression patterns, which underlie a variety of human maladies, including all cancers. Epigenetic aberrations have been shown to contribute to all stages of oncogenesis from initiation to metastasis. Understanding how epigenetic circuits are established, maintained and inherited at the molecular level is critical for the development of novel targets and therapeutic tools in the battle against cancer. Most of what is known about the molecular mechanism of epigenetic inheritance comes from decades of research in model organisms such as Saccharomyces cerevisiae, Schizosaccharomyces pombe, and Drosophila melanogaster. This research has led to the discovery of highly conserved protein families and chromatin marks which are now being targeted for therapeutic or diagnostic purposes.

Noncoding RNAs and chromatin

The first model about how long and small noncoding RNAs mediate epigenetic inheritance of chromatin states was proposed in the fission yeast. Our model posits that noncoding RNAs, tethered to chromatin, provide a platform for the assembly of RNA-processing and chromatin-modifying proteins, leading to transcriptional regulation of the neighboring genes. In addition to acting as platforms, RNA molecules target chromatin regulatory proteins to specific chromosomal regions. These principles now have emerged as a conserved mechanism by which noncoding RNAs partake in epigenetic inheritance of chromatin states and regulate gene expression globally. Recent work in cancer has revealed that regulation of epigenetic states by noncoding RNAs is intimately associated with all stages of oncogenesis. Thus uncovering the molecular details of this mechanism is one of the most promising fields of research in molecular biology.

In the Motamedi lab, we study how noncoding RNAs and chromatin complexes cooperate to mediate epigenetic gene silencing. We use a combination of genetic, biochemical, cell
The image on the left depicts RNA-mediated epigenetic gene silencing at the fission yeast centromeres, during which nascent long non-coding (lnc) RNAs, tethered to chromatin, act as platforms for the recruitment of silencing proteins. New synthesis of lncRNAs (shown as incorporation of new ribonucleotides) followed by lncRNA processing into short siRNAs (yellow RNA in the red complex) lead to amplifications of the RNA silencing signal. The image on the right depicts the polymerization domain of one of the key silencing proteins, Tas3. This self-polymerization property is required for the ‘spreading’ of silencing factors from initiation centers to the surrounding chromosomal regions. This mechanism is required for proper chromosome segregation and maintenance of genomic stability.

biological, genomic and proteomic approaches to ask mechanistic questions about how epigenetic states are established, maintained and reprogrammed in cells. Because many of the proteins involved in this process are highly conserved among eukaryotes, we will apply this knowledge to investigate how the homologous proteins regulate epigenetic inheritance in human cancers. For example, latest data from the lab have identified several chromatin and noncoding RNAs whose genome-wide rearrangements in response to stress play a central role in adaptive responses. This work has revealed a novel function for these proteins and noncoding RNAs, and appears to be conserved from yeast to human cells.

DNA repair and genomic stability

Another interest of the Motamedi lab is DNA repair and genome stability. In eukaryotic cells, the abundance of repetitive DNA sequences (centromeres, telomeres, rDNA, etc.) and the presence of an efficient recombination system pose a serious challenge to genomic stability. Aberrant recombination among repetitive DNA elements results in loss or duplication of genetic information often contributing to an increase in mutation rates and genome instability. To maintain genomic stability, cells compact their repetitive DNA into a special structure called heterochromatin, which prevents spurious recombination among repeats, thus stabilizing the genome. Cells defective in heterochromatin formation exhibit high rates of chromosome loss in mitosis, genomic instability, and increased mutation rates. In cancers, heterochromatin is lost in nearly all cancers contributing to their increase in mutation rates and cancers. In the Motamedi lab, we study how chromatin and noncoding RNAs cooperate to maintain heterochromatin and genomic stability. Our goal is to gain novel insight into the conserved mechanisms by which cells make their repetitive DNA elements refractory to recombination and regulate the access of these factors to these regions. Overall our goal is to harness the powerful genetic, biochemical, and cell biological tools available in the fission yeast to drive novel discoveries in pathways affected in cancers.

Selected Publications:


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†This article was previewed in Dev Cell. 16: 630-632, 2009
††This paper was featured as the cover article