

Mo Motamedi, PhD



Motamedi Laboratory

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Research in **the Motamedi laboratory** focuses on a molecular memory system, called epigenetics, which allows cells to develop distinct identities during development or become resistant to different types of stress such as chemotherapy. Epigenetic states are formed when groups of genes are turned on and off at a given time in a given cell. Recent work has shown that cancer cells exploit epigenetic mechanisms to develop resistance to radiation, chemo- or immune-therapy. By studying the molecular machinery that establish epigenetic states in model organisms, the Motamedi lab has identified a critical pathway that helps cancer cells establish resistance to therapy. By inhibiting this pathway, they aim to reverse chemotherapy resistance stably in several cancers. This discovery will help in addressing this difficult unmet need in cancer therapy.

Epigenetic changes are heritable, phenotypic alterations which occur without mutations to the underlying genes. Once triggered, these phenotypic changes persist through numerous cell divisions independently of the original inducing signal. Epigenetic changes are critical for the stable formation of cellular identities, upon which all developmental processes depend. Disruption to epigenetic regulation underlies a variety of human maladies, including cancers. In fact, epigenetic pathways can contribute to all stages of cancer progression, including initiation, metastasis, resistance and recurrence. Indeed, understanding the molecular mechanisms that establish epigenetic states is fundamental to the development of therapies that target the epigenetic components of cancers.

Often, but not always, epigenetic changes are concomitant with alterations to the chromatin state of underlying genes. Most of what is known about how chromatin states are altered in response to epigenetic triggers comes from decades of research in model organisms. These studies have revealed highly conserved protein families, which are now used for therapeutic or diagnostic

purposes in cancers. The Motamedi lab uses the fission yeast as a model to understand how changes to eukaryotic chromatin are made, maintained and propagated, and how these changes establish alternative transcriptional programs particularly in response to persistent stress.

Noncoding RNAs and chromatin – partners in epigenetic regulation

One of the first models for how long and small noncoding RNAs regulate chromatin states was proposed in the fission yeast. It posits that noncoding RNAs, tethered to chromatin, provide a platform for the assembly of RNA-processing and chromatin-modifying proteins (Motamedi et al 2004), leading to transcriptional regulation of the underlying genes. These principles now have emerged as conserved mechanisms by which noncoding RNAs partake in chromatin regulation in eukaryotes including in humans.

A focus of the lab is cellular quiescence (or G0). G0 is a ubiquitous cellular state in which cells exit proliferation and enter a state of reversible dormancy. Developmental programs, such as wound healing, or exposure to a variety of stress,



The image depicts as cells enter quiescence (moon), they load Ago1 (ships) with euchromatic small RNAs to mediate Quiescent-induced Transcriptional Repression (Q) of a set of euchromatic genes. Exosome activity separates heterochromatic (dark blue) from euchromatic (yellow) regions. When entering quiescence, the exosome barrier opens, permitting euchromatic transcripts (differently colored dots) to become substrates for RNAi degradation. Ago1, acquiring new color (sRNAs) as it crosses the exosome barrier, targets Q to the corresponding color in euchromatin.

such as starvation, can trigger entry into or exit from G0. G0 cells have distinct transcriptional programs through which they acquire new properties compared to their proliferative selves, including long life, thrifty metabolism and resistance to stress. Loss of G0 regulation results in defects in developmental and adaptive programs. How cells enter, survive and exit G0 is a critical question in basic biology, which is largely unexplored. To address this knowledge gap, we modeled G0 in fission yeast and showed that when cells transition to G0, new ncRNAs emerge which coopt and deploy constitutive heterochromatin proteins (histone H3 lysine 9 methyltransferase, Clr4/SUV39H) to several euchromatic gene clusters to regulate the expression of a set of developmental,

metabolic and cell cycle genes. We show that this pathway is critical for survival and the establishment of the global G0 transcriptional program. This work revealed a new function of heterochromatin proteins and noncoding RNAs, which orchestrate the genome-wide deployment of heterochromatin factors in response to long-term stress. It also led to the proposal of several hypotheses that we are currently testing. Moreover, in collaboration with several groups, we have begun to test whether this pathway also plays an important role in cancer dormancy and treatment resistance.

Selected Publications:

Calvo I A, Sharma S, Paulo JA, Gulka A, Boeszoermenyi A, Zhang J, Lombana JM, Palmieri CM, Lavolette LA, Arthanari H, Iliopoulos O, Gygi SP, **Motamedi M**. The fission yeast FLCN/FNIP complex augments TORC1 repression or activation in response to amino acid (AA) availability. *iScience*. 2021. 24(11), 103338.

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Li H*, **Motamedi M***, Yip C, Wang Z, Walz T, Patel DJ, Moazed D. An alpha motif at Tas3 C terminus mediates RITS cis-spreading and promotes heterochromatic gene silencing. *Mol Cell*. 2009; 34: 155-167.

Motamedi M, Hong EE, Li X, Gerber S, Denison C, Gygi S, Moazed D. HP1 proteins from distinct complexes and mediate heterochromatic gene silencing by non-overlapping mechanisms. *Mol Cell*. 2008; 32: 778-790.

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**This article was the cover story in *Cell*