Research Interests – Dr. Asifa Akhtar

Every cell in the human body has the same genetic information, collectively known as the genome. In spite of this, your body is composed of highly specialized organs with distinct functions, for example, the heart or brain. At the molecular level, we know that functional biomolecules, RNA and proteins, are responsible for the phenotypic differences between these organs. Since the genome contains instructions for the synthesis of all RNA and proteins, this begs the question of how the organism chooses which ones are produced by a particular cell at a given time. Understanding how genetic information is decoded in our cells is the central question driving research in my lab.

A cell's choice to produce a particular RNA or protein is driven by epigenetic regulation. In simple terms, epigenetics is the study of changes in gene expression, which are not caused by changes in the DNA sequence. If phrased in an analogy, the genome is a cookbook filled with recipes (genes), and the epigenetic regulator is the chef responsible for choosing the recipe and for opening or closing and bookmarking the book at the appropriate page, which either facilitates or prevents the recipe from being read.

My lab is interested in the molecular components and mechanisms driving epigenetic regulation. More specifically, I am fascinated by epigenetic regulation through histone acetylation and large non-coding RNAs. Histones are proteins that are intimately associated with and regulate access to the genome. Histone acetylation refers to the addition of a chemical label to these histone proteins that acts as a signpost or marker to indicate to the cell which gene should get expressed.

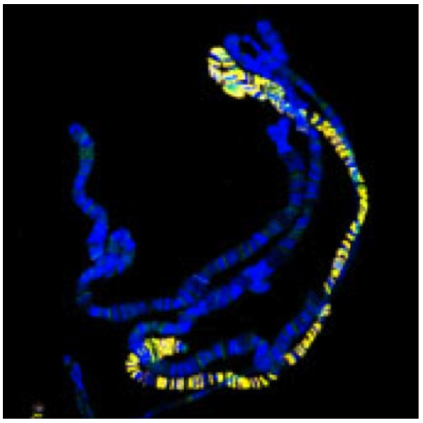
A fascinating process regulated by epigenetics is the equalisation of the sex chromosomes. Human males carry one X and one Y chromosome, whereas females carry two Xs. Most of the genes on the X chromosome are in fact essential for both males and females. To address the imbalance between the sexes, human females shut down one of their X chromosomes in order to make the "dose" of active X chromosome genes equal to that in males. The same imbalance is also observed in fruit flies, a favourite model organism for biologists. Fruit flies have devised an alternative way, by doubling the output of the single male X chromosome to make it equal to that of the two X chromosomes in females. This phenomenon is termed dosage compensation and relies on hyperacetylation of the active X chromosome by

the histone acetyltransferase MOF. MOF is part of a ribonucleoprotein complex known as the dosage compensation complex (also known as the MSL complex) that decorates the male X chromosome, thus providing an exquisite specificity and precision to the two-fold upregulation of gene expression. The lab is committed to increasing our understanding of the mechanistic principles behind how choice, decision and memory of X chromosome regulation is achieved.

Although well known for its function on the X chromosome, our lab has shown that MOF also regulates genes on autosomes by participating in a separate protein complex known as the NSL complex (Fig 1). Furthermore, the lab has found that both the NSL and MSL complexes are conserved through evolution from flies to humans. Thus, revealing that MOF plays a much broader role in gene regulation than previously anticipated in both flies and mammals.

The contribution of RNA to epigenetic regulation remains an exciting area of biology. The intimate association of the roX long-coding RNAs in X chromosome regulation provides a paradigm of a biological phenomenon that is not only critical for survival but also where we can systematically study the molecular mechanism. In future, we will continue to explore this in more detail.

Although histone acetylation is not the only mode of epigenetic regulation, an aspect that makes it particularly fascinating is that it can respond very rapidly to alterations in cellular state. In particular, histone acetylation is known to change according to the cellular metabolic state and thus could be influenced by environmental changes or diet. Whereas epigenetic regulation typically takes place in the cell nucleus (where the genome is contained), the metabolic hub, also known as the “powerhouse” of the cell, is the mitochondria. Mitochondria harbour a mini genome carrying genes encoding several important metabolic proteins.



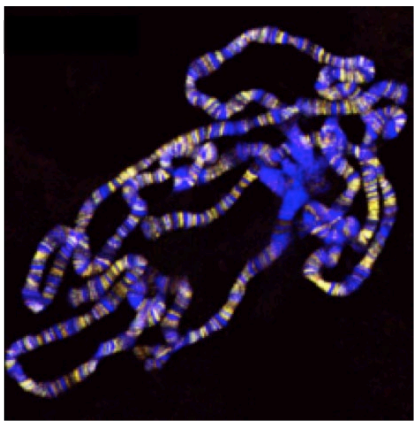


Fig 1 Chromosomal spreads from salivary glands of male fruit fly larvae. Left image: The X chromosome is decorated by the MSL complex (in yellow), the other chromosomes can be seen in blue. Right image: The NSL complex (in yellow) is spread across both the X chromosome and the autosomes.

We recently uncovered that the histone acetyltransferase enzyme MOF, classically associated with regulating the genome in the nucleus, can also be found in the mitochondria. Furthermore, we found that the enzyme regulates transcription from the mitochondrial genome, enabling it to rapidly influence the metabolic pathways of the cell. The regulation of metabolism by the MOF enzyme is critical to cell function. Cells, which have a high metabolic rate such as the heart, cannot survive without MOF. This makes MOF a central player in the communication between the cell's epigenetic and metabolic states. This metabolic-epigenetic interface is important for cells to adapt to changing conditions and stresses. We are interested in understanding how MOF is able to sense the metabolic state of the cell and how its targets and response vary between cell types.

A major current aim of my lab is to understand the deregulation of the MSL and NSL complexes in human disease. Indeed, we have recently characterised a new human syndrome with de novo mutations in MSL3 that affects histone H4 lysine 16 acetylation. The mechanistic insights that we had gained from studying the MSL proteins in flies helped us to pinpoint the molecular nature of the defect observed in these patient cells. In the future, the lab will continue to combine molecular and physiological insights across species to understand the many facets of epigenetic regulation by histone acetylation.