Mechanism and function of autosomal analog of X inactivation

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Autosomal monoallelic expression (MAE) is a recently discovered epigenetic phenomenon that controls the relative expression of maternal and paternal alleles in a large fraction of human genes. The way the active allele is randomly chosen and then stably maintained due to MAE resembles X chromosome inactivation, though MAE affects genes in both male and female cells. MAE can profoundly affect cell fate, causing two sister cells within the same individual to perform in diametrically opposite ways, depending on whether the normal or mutant allele of the gene is active. Understanding the function and mechanism of MAE should significantly contribute to revealing the precise link between specific gene variants and susceptibility to a variety of disorders.

Genes subject to MAE are implicated in major diseases including cancer, autism, and Alzheimer's disease, promising that MAE research will have a significant impact on multiple fields of biomedicine. However, progress in understanding mechanistic and functional aspects of MAE has been hindered by the inadequacy of traditional technological approaches, which don't allow for systematic analysis of a mechanism that inherently generates enormous cell-to-cell variation. This epigenetic heterogeneity masks variation in allelic expression in contexts where cells are analyzed in bulk, such as most genome-wide and high-throughput research strategies. As a result, researchers have lacked basic knowledge or even the tools for efficiently generating this knowledge.

In response, we have developed and validated several pioneering methods that circumvent this barrier, and enable accurate and precise assessment of MAE in human cells and tissues and allow us to conduct systematic functional, mechanistic, and genetic studies of MAE. We use several novel technologies to directly address critical questions about MAE biology. We will dissect the molecular mechanisms involved in MAE initiation, development, and stable maintenance over multiple cell divisions in human cells, opening the door to targeted manipulation of allelic activity. We also address the following fundamental functional questions about effects of MAE: How prevalent is MAE in an organism *in vivo*? How does it vary between individuals? What are the functional consequences of widespread MAE?

Successful completion of this project will provide crucial knowledge for precise interpretation of genotype-phenotype relationship in the context of human normal development and disease. It will also bring new understanding of cell-to-cell and between-individual variability. These insights may be translated into diagnostic, preventative, and therapeutic treatments in the context of personalized medicine.