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Stable Autosomal Monoallelic Expression Is Maintained By Multiple Mechanisms

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Widespread autosomal monoallelic expression (MAE) affects thousands of mammalian genes in a manner resembling X-chromosome inactivation (XCI). Similar to XCI, MAE results in an epigenetic mosaic, with clonal cell populations showing highly stable transcriptome-wide patterns of full or partial allelic silencing. In contrast to XCI and genomic imprinting, very little is known about the mechanisms involved in allelic silencing of genes subject to MAE. To identify perturbations that can disrupt silencing during MAE, we have developed a systematic screening approach, Screen-seq ASE. This multi-well screening approach is based on targeted RNA sequencing at dozens of MAE loci. Changes in allele-specific expression (ASE) are assessed using existing polymorphisms in cDNA, obviating the need of introducing extrinsic reporters into the cells. We have previously characterized MAE in monoclonal B-cell lines from mice with a high density of polymorphisms (129xCast F1). For our screen, we assessed changes in ASE for 28 genes in one such cell line in response to a collection of 48 drugs known to affect epigenetic targets. In 3 of 28 genes tested, exposure to the DNA methylation inhibitor 5-aza-deoxycytidine reactivated the silenced alleles. The extent of reactivation is dose and time-dependent. Partial reactivation of the same genes was also observed in response to knock-down of Dnmt1, consistent with the role of DNA methylation in MAE maintenance in some loci.

Our multi-locus screening strategy has allowed us to identify, for the first time, a perturbation that reactivated alleles stably silenced due to MAE. For a subset of these genes, the maintenance of allelic silencing depends on the DNA methylation state. Transcription of other genes remained monoallelic, suggesting that MAE maintenance in different loci depends on distinct mechanisms.

Conclusion:

In 3 of 28 genes tested, exposure to the DNA methylation inhibitor 5-aza-deoxycytidine reactivated the silenced alleles. The extent of reactivation is dose and time-dependent. Partial reactivation of the same genes was also observed in response to knock-down of Dnmt1, consistent with the role of DNA methylation in MAE maintenance in some loci.

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