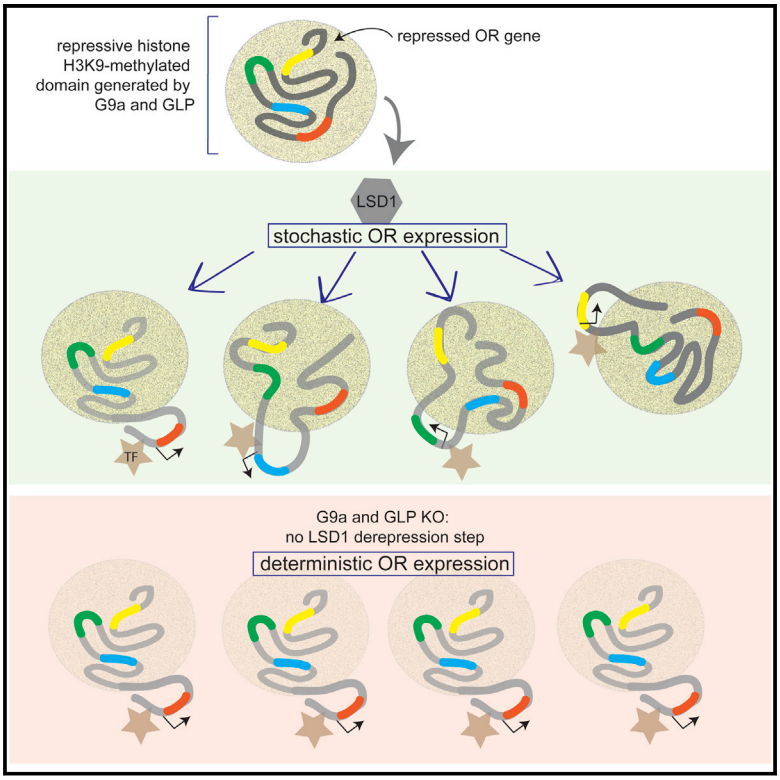
Report

Cell Reports

Heterochromatin-Mediated Gene Silencing Facilitates the Diversification of Olfactory Neurons

Graphical Abstract



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In Brief

Olfactory receptor (OR) genes become marked by constitutive heterochromatin during early olfactory neuron differentiation. Lyons et al. now show that histone methyltransferases G9a and Glp govern the heterochromatic silencing of OR genes, which is essential for diverse and singular OR expression.

Highlights

G9a and GLP help to generate stochastic olfactory receptor (OR) choice

OSN diversity exhibits a G9a/GLP dose dependency

The "one receptor per neuron" rule is violated in the absence of G9a and GLP

Loss of H3K9me3 at OR clusters impairs OR nuclear topology

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Heterochromatin-Mediated Gene Silencing Facilitates the Diversification of Olfactory Neurons

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SUMMARY

An astounding property of the nervous system is its cellular diversity. This diversity, which was initially realized by morphological and electrophysiological differences, is ultimately produced by variations in gene-expression programs. In most cases, these variations are determined by external cues. However, a growing number of neuronal types have been identified in which inductive signals cannot explain the few but decisive transcriptional differences that cause cell diversification. Here, we show that heterochromatic silencing, which we find is governed by histone methyltransferases G9a (KMT1C) and GLP (KMT1D), is essential for stochastic and singular olfactory receptor (OR) expression. Deletion of G9a and GLP dramatically reduces the complexity of the OR transcriptome, resulting in transcriptional domination by a few ORs and loss of singularity in OR expression. Thus, our data suggest that, in addition to its previously known functions, heterochromatin creates an epigenetic platform that affords stochastic, mutually exclusive gene choices and promotes cellular diversity.

INTRODUCTION

Stochastic gene expression is important in generating the diverse cell types of the nervous system. The *Drosophila* Dscam family of alternatively spliced isoforms (Zipursky et al., 2006), photoreceptor choice in mammals and flies (Rister and Desplan, 2011), cellular differentiation within motor neuron pools in the spinal cord (Dasen et al., 2005, 2008), and the choice of mammalian protocadherin promoters (Chen and Maniatis, 2013) all provide examples of nondeterministic gene-expression programs with critical roles in the generation of neuronal diversity (Chen et al., 2012; Lefebvre et al., 2012). However, the monogenic and monoallelic expression of a single olfactory receptor (OR) gene (Chess et al., 1994) from more than 1,000 available alleles (Buck and Axel, 1991) provides the most-extreme paradigm of stochastic transcriptional choice that determines the fate, circuitry, and functional identity of an olfactory sensory neuron (OSN).

The molecular mechanisms of OR gene choice in mammals remained unknown until the identification of a feedback signal that stabilizes the expression of the chosen OR allele and prevents the transcriptional activation of additional alleles (Lewcock and Reed, 2004; Serizawa et al., 2003; Shykind et al., 2004). This feedback, which is generated by the OR protein-dependent activation of the ER-resident kinase Perk, leads to transient translation of transcription factor Atf5 and downregulation of histone demethylase LSD1 (Dalton et al., 2013; Lyons et al., 2013). LSD1 activates OR transcription most likely via the demethylation of lysine 9 of histone H3 (Lyons et al., 2013), an epigenetic mark that is deposited on OR genes at the early stages of OSN differentiation, along with histone H4 lysine 20 trimethylation (Magklara et al., 2011).

These observations suggest that the heterochromatic silencing of OR genes plays an important role in singular and stochastic OR expression. First, it keeps the nonchosen ORs completely silent, thereby ensuring coherent neuronal targeting and activity. Second, it affords a feedback process, which "silences the desilencer" and thus prevents activation of additional ORs without affecting the expression of the already chosen allele. It is not clear from these data, however, whether H3K9 demethylation, ostensibly required based on the effects of LSD1 deletion, is also sufficient for OR transcription. In other words,