Molecular Cooperativity Leads to Monoallelic Olfactory Receptor Expression

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***Short Abstract* — Each mammalian olfactory sensory neuron expresses only one out of thousands of olfactory receptor alleles and the molecular mechanism remains as one of the biggest puzzles in neurobiology. We constructed a mathematical model and identified a three-layer regulation mechanism that robustly generates single-allele expression: zonal separation, epigenetic activation and subsequent allele competition for a limited number of enhancers. Model analyses conclude that the regulatory system has been evolutionarily optimized to minimize multiple allele activation and alleles trapped in incomplete epigenetic activation states. The identified design principles demonstrate the importance of molecular cooperativity in selecting and maintaining monoallelic olfactory receptor expression.**

I. INTRODUCTION

Olfaction is essential for the proliferation and survival of an organism. One of the most intriguing puzzles in neurobiology that remains elusive after several decades of intensive investigations is: how is a single allele selected for activation from a large number of possible OR genes and maintained throughout the lifespan of the neuron? Proposals on the selection mechanism can be divided into two categories: individual-allele centered selection, and enhancer-regulated selection. Each of the two proposed mechanisms has experimental supports and complications. The individual-allele epigenetic competition model reveals a natural feedback mechanism that expression of the winning allele causes endoplasmic reticulum stress and expression of Adcy3 enzyme, which then down-regulates LSD1, leading to an epigenetic trap that stabilizes the OR choice [1]. Multiple enhancers bind to the active OR alleles, but not the silenced ones, and form a dense interaction network [2]. The present work aims to reconcile the above two models and provides a mechanistic explanation on single-allele OR expression.

II. MODEL AND RESULTS

We formulated a mathematical model for the OR activation problem. First, zonal segregation reduces the number of OR alleles competing for single allele expression from thousands to hundreds within a zone. We therefore modeled a cell with 100 alleles to recapitulate the selection process from within a single zone of olfactory epithelium. Each OR allele consists of a linear array of 41 nucleosomes, and each nucleosome can bear repressive H3K9, no, or active H3K4 methylations [3]. Transition between these states is governed by enzyme concentration dependent rates.

We first examined the model under conditions prior to and after OSN differentiation. We found that maintaining high levels of methyltransferases and low level of demethylases forces an allele to be kinetically trapped at one of the two possible epigenetic states throughout the life time of an OSN.

Second, we found that elevation of bifunctional demethylase level leads to a barrier-crossing like dynamics and most of the OSNs with one allele epigenetically activated while a small fraction has two and rarely 3 alleles epigenetically activated. A prominent feature of this barrier-crossing-like dynamics is that throughout the process the probability of having an allele with hybrid pattern of epigenetic marks is low, and most alleles only fluctuate around the H3K9me3 dominated state.

Third, we found that the epigenetic conversion mechanism is insufficient to explain the experimental results on inhibiting methyltransferases/demethylases unless we added another layer with cooperative enhancer competition. We predict a loss of diversity of OR expression when the level of H3K9 methyltransferases is reduced, which is consistent with what observed experimentally [4].

III. DISCUSSION & CONCLUSION

Our theoretical studies suggest that single allele activation may be achieved through a series of selection processes functioning synergistically. A subset of the alleles is selected by the zonal segregation. Then they are randomly chosen to be epigenetically activated though elevation of bifunctional LSD1. Most of the cells only have one epigenetically active and thus transcriptional active allele. If more than one allele are epigenetically activated, they compete for the enhancers to be transcriptionally active, resulting in only one epigenetically and transcriptional active allele. If the activated allele is not pseudo gene, it triggers the feedback to prevent further epigenetic state change.

Acknowledgements: The research was supported by the U.S. National Science Foundation (DMS-0969417).

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