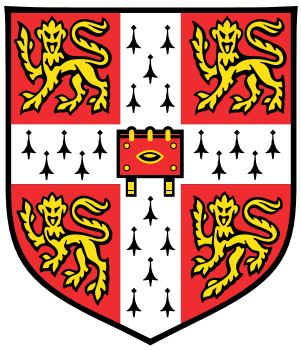
Genetic and environmental regulation of olfactory sensory neurone diversity



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To mom and James for being there every step of the way.

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration, except where specifically indicated in the text. This dissertation contains fewer than 60,000 words excluding bibliography, figures and appendices, as per the requirements of the Degree Committee for the Faculty of Biology.

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Abstract

Animals use their sense of smell to gather plethora of information about their surroundings. The detection of odorants occurs in the main olfactory epithelium (MOE), which contains olfactory sensory neurones (OSNs) among other cell types; these express olfactory receptors (ORs) that bind to odorants. Each OSN expresses only one allele of one OR gene from a family of over 1,200 in the mouse genome. Thus, the mouse nose has over 1,200 different OSN types, each characterised by the OR expressed. High levels of genomic variation have been reported both in the mouse and human OR repertoire. This is thought to contribute to the unique sense of smell each individual has, but a large proportion of the observed phenotypic variance remains unaccounted for.

In this dissertation, I present the results from an RNAseq-based approach used to quantify the OSN repertoire of the mouse. Firstly, I validated the accuracy and reproducibility of this technology to study the olfactory system. I then characterised the transcriptome of the MOE and of the OSNs as a population and at the single-cell level. This allowed me to conclusively prove that OR expression is indeed monogenic and monoallelic. Then, I demonstrated that the method is sensitive enough to detect the expression of almost the complete OR repertoire. Also, I was able to annotate full-length gene models for many OR genes.

Secondly, I explored the diversity of OSN types in three inbred strains of mice (C57BL/6, CAST/EiJ and 129S5) via their OR gene expression levels. I found that each strain has a unique and reproducible distribution of OSNs in their noses, and that genomic variation instructs this neuronal variance in *cis*. Finally, I analysed the plasticity of the distribution of the different classes of OSNs by stimulating animals with particular odorants. Exposure to an enriched olfactory environment results in the differential expression of dozens of OR genes in a reproducible and specific manner. These changes increase with time and are reversible. These data allow to comprehensively explore and dissect the effects of genetic and environmental variation on the regulation of OR expression and OSN repertoire. Together they generate an olfactory sensory system that is individually unique.

Contents

List of Figures

List of Tables