Investigating the role of Histone Deacetylase HDAC4 in long-term memory formation

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ABSTRACT

Epigenetic mechanisms are emerging as master regulators of cognitive abilities such as learning and memory. It has been previously shown that the histone deacetylase HDAC4 plays a critical role in memory formation in both mammals and insects although the specific mechanisms through which it acts have not yet been elucidated. HDAC4 undergoes nucleocytoplasmic shuttling and, in neurons, it is largely cytoplasmic implying it may play both nuclear and non-nuclear functions. To identify upstream regulators and downstream targets of HDAC4, a genetic interaction screen was performed in the fruit fly Drosophila melanogaster, a powerful model system to study the genetic mechanisms of neurological disease. Twenty-nine genes were found to interact with HDAC4 suggesting they are part of the same molecular pathway. Functional network analysis revealed that many of the genes could be grouped into three biological categories comprising transcriptional factors, SUMOylation machinery enzymes and cytoskeletal regulators/interactors. Within the latter, Ankyrin2 was selected for further analysis as it is implicated in synaptic stability and in human intellectual disability. In addition HDAC4 harbours a conserved ankyrin binding domain. Immunohistochemical analyses showed widespread distribution of Ankyrin2 throughout the adult brain and coincident distribution with HDAC4 was observed in the axons of the mushroom body, a key structure for memory formation in flies. Both HDAC4 and Ankyrin2 were also found to regulate mushroom body development. RNAi-mediated depletion of Ankyrin2 in the adult brain impaired long-term memory in the courtship suppression assay, a model of associative memory and preliminary evidence of a physical association between HDAC4 and Ankyrin2 was also demonstrated. The genes identified in the screen provide new avenues for investigation of the mechanisms through which HDAC4 regulates memory formation and preliminary analyses suggest that interaction with the cytoskeletal adaptor Ankyrin2 may involve remodelling of the actin/spectrin cytoskeleton, phenomenon that underlies memory related processes like synaptic plasticity and neuronal excitability.
ACKNOWLEDGEMENTS

This was the year of the Summer Olympic Games and I could not help the feeling of participating to a sort of Olympic Games myself… as a PhD student. In particular, this sport event corresponded exactly with my thesis writing and made me realise that academic life and sport training share similarities. As in sport training, the good days are rare. Most of the time, it is hard, it takes a long time, things go wrong, better and then wrong again and in order to be successful at either, your commitment must be to the process, not to the final prize. However, with dedication, passion, patience and a good dose of optimism the final goal would gradually approach.

Firstly, I would like to express my gratitude to my supervisor Dr Helen Fitzsimons for the endless support, encouragement and the inestimable enthusiasm for my project. Being trained and mentored by someone who really understands the “sport” is an amazing experience and I am in awe of your depth of knowledge and optimism that helped me during the most difficult days. You taught me that every day is a good day because there is something new to learn. An immense appreciation goes to my co-supervisors, Professor Kathryn Stowell and Dr Tracy Hale for their massive knowledge, precious advice and suggestions, and for their priceless availability and dedication. Yes… I have been a very lucky student.

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I always believe that after a wonderful and rich experience ‘the best is yet to come’… Well, it will be very hard to exceed what I experienced here in New Zealand but I will do my best to, at least, get close to that.

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<th>Full Form</th>
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<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>AIS</td>
<td>Axon initial segment</td>
</tr>
<tr>
<td>Ank1</td>
<td>Ankyrin1</td>
</tr>
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</tr>
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<tr>
<td>ANK-R</td>
<td>Ankyrin R</td>
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<tr>
<td>Arc1</td>
<td>Activity-regulated cytoskeleton associated protein 1</td>
</tr>
<tr>
<td>Att</td>
<td>Arginine tolerance test</td>
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<tr>
<td>Aβ</td>
<td>Amyloid-beta</td>
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<td>BDSC</td>
<td>Bloomington Drosophila Stock Centre</td>
</tr>
<tr>
<td>bp</td>
<td>Base pair</td>
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<tr>
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<td>Calcium</td>
</tr>
<tr>
<td>CaMK</td>
<td>Calcium/calmodulin-dependent kinase</td>
</tr>
<tr>
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<td>Cyclic adenosine monophosphate</td>
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<td>Complementary DNA</td>
</tr>
<tr>
<td>CI</td>
<td>Courtship index</td>
</tr>
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<td>CIP</td>
<td>Calf intestinal alkaline phosphatase</td>
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<tr>
<td>Cm</td>
<td>Centimeters</td>
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<td>cAMP response element</td>
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<td>cAMP response element binding protein B</td>
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<td>Canton special</td>
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<td>Deoxyribonucleic acid</td>
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<td>Drosophila interactions database</td>
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<td>Ethylenediaminetetraacetic acid</td>
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<tr>
<td>EGFP</td>
<td>Enhanced green fluorescent protein</td>
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<tr>
<td>EGTA</td>
<td>Ethylene glycol tetraacetic acid</td>
</tr>
<tr>
<td>Elav</td>
<td>Embryonic lethal abnormal visual system</td>
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<td>Full Name</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>FasII</td>
<td>Fasciclin II</td>
</tr>
<tr>
<td>FLIM</td>
<td>Fluorescence lifetime imaging microscope</td>
</tr>
<tr>
<td>FPKM</td>
<td>Fragments per kilobase of transcript per million mapped</td>
</tr>
<tr>
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</tr>
<tr>
<td>GFP</td>
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<tr>
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<td>Glass multimer reporter</td>
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