Epigenetics of obesity and functional characterization of a novel motif through the analysis of locomotory behavior in mice

The World Health Organization has placed obesity as the fifth leading global health risk. Approximately 2.8 million adults die each year as a result of being overweight or obese. Obesity was thought to be a psychological disorder, but this view has changed over the last decade. Genome wide association studies compare the complete DNA of people with or without a disease and aim to find genes that behave differently that can be associated with those diseases. Recent whole genome studies have found genes associated with obesity and other associated disorders like type 2 diabetes. One such study, relates a common variant of the FTO gene with methylation (modification of DNA wherein a methyl ($-CH_3$) group is added to the cytosine residues and hence affects gene behavior) pattern in a certain part of that gene to type 2 diabetes.

In our project we aim to establish a similar relation in the case of obesity. We had 47 patient DNA samples, which had been typed for above-mentioned common variant. These subjects had been categorized with based on their BMI into normal (BMI between 18-25) and overweight (BMI>25). Sequencing a small portion of the FTO gene for methylation would show if the methylation in this region is associated with the common variant and obesity. Problems with optimizing the sequencing primers proved to be difficult to overcome and the samples got degraded in the meantime. Though the project could not be completed, the process of troubleshooting helped in improving knowledge about the technicalities of sequencing and primer design.

The cell is the basic functional unit of life. Cell membrane is that part of the cell which defines its boundaries and protects it from the external environment. Proteins form a large part of this membrane and help the cell interact with the external environment. Solute carriers (SLC's) are proteins that help with the transport of molecules into the cell in a selective manner. These SLC's form a very important part of excitatory (like dopamine, glutamate) and inhibitory (like γ-amino butyric acid i.e. GABA) pathways in the brain. Previously in our lab, we have found a novel putative SLC (named as SLCZ1), hypothesized to be involved in GABA system. Its function could be the transport of glutamate into the brain cells involved in GABA pathway where glutamate would be used to make GABA.

We generated a line of mice in which SLCZ1 has been rendered non-functional with the help of genetic manipulation, which should lead to low GABA levels in the brain. Locomotion is an observable behavior that can be used to indirectly measure the amount of GABA. We use amphetamine, a drug that induces dopamine release and hence increases locomotion. This in combination with low GABA (due to lack of glutamate in the conditional knockout mice) should give an increase in the locomotory activity of genetically engineered mice in comparison to the wildtype counterpart. In this project I compared the locomotory behavior of the conditional knockout and wildtype mice in response to different doses of amphetamine. The activity of the conditional knockout mice was highly raised in comparison to the wildtype mice for 4mg/kg dose of amphetamine. This result showed that SLCZ1 could be involved in the GABA signaling.

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