

The role of lipoproteins and lipoprotein receptors in mediating the effects of childhood trauma on the brain and the germline

Many aspects of adult human health are determined by the quality of life during childhood. Exposure to adverse conditions during childhood can lead to increased predisposition to several physical and mental health ailments during one's adult life. It has also been shown that sometimes the risk of such physical and mental disturbances can even be passed on from one generation to the next. The persistence and transmission of such effects is hypothesised to involve complex interactions between the genes of an individual and the adverse environmental conditions. When the expression of genes relevant to control of behaviour is altered in the brain, it manifests as behavioural perturbations, such as depressive behaviours. Similarly, when the expression of genes is altered in germ cells (sperm and eggs), the effects can be passed onto the children of the affected individual.

Previous research from our lab showed that childhood trauma in humans, as well as modelling of childhood trauma in mice changes factors that control expression of genes in both the brain and the germ cells. However, it remains unclear how the effects of emotional trauma that is perceived at the behavioural level persist for so long, affect other body organs, and are carried to the germ cells. Fats present in the blood appear as important factors that can carry the abnormalities caused by trauma via the blood to the germ cells. They could be relevant because it is already known that the composition of fats is altered in the blood of both animals and humans who had adverse conditions early in life. Interestingly, these fats can bind special molecules called non-coding RNAs, which can control the expression of genes. Thus, these fats can preserve the signatures of trauma over a long time and cause behavioural abnormalities later on and even deposit these in the germ cells for transmission to the next generation.

A major aim of this study is to investigate if body fats are involved in carrying the effects of trauma to the brain and the germline line. As a part of this, we will check if the non-coding RNAs bound to body fats are altered by childhood trauma and if these changes persist till adulthood using two different cohorts. Then we will investigate if stimulating laboratory models of brain and germ cell development are altered when stimulated with body fats from traumatised individuals. Finally, we will validate our idea by blocking the uptake of these body fats by the developing brain and germ cell laboratory models.

We have identified and assembled two populations with documented evidence of childhood trauma. One group comprises children between the age of 7 to 12 years who experienced trauma in the form of the demise of their fathers and separation from mothers (paternal loss and maternal separation: PLMS). The other group comprises adult men who witnessed genocide in Bosnia and Herzegovina during the age of 7-12 years. As a first step, body fats will be derived and purified from the blood samples of both these groups. Then, non-coding RNAs bound to the purified body fats will be analysed and validated through robust molecular biology methods. After confirming that there are changes in the non-coding RNAs bound to these purified body fats in association with childhood trauma, we will check their effects on laboratory models of brain and germ cells. To test the effects on the brain, we will use a model of brain organoids, which are derived from human stem cells and capture the developmental stages of the brain from conception till adulthood. Similarly, to test the effects on the germ cells, we will use testicular organoids, which represent the biological environment of male reproductive tract. Both these models will be treated with the body fats derived from the trauma groups and comprehensively assessed for changes in expression and function of genes relevant for behaviour and metabolism. Finally, we will use a novel editing tool to modify the brain and testicular models in a way that they become resistant to uptake of body fats. If this modification prevents changes in the gene expression and function of brain and germ cells after treatment with body fats from traumatised individuals, it will provide further proof that body fats are responsible for transmitting the effects of trauma.

Based on our previous work, we anticipate that microRNAs in lipids isolated from serum will differ between control group and individuals exposed to childhood trauma. Lipids isolated from people exposed to trauma will have a different impact on the brain organoids than lipids from the control group. Using the gene editing tool we will obtain cells without a receptor for studied lipids. Modified cells will not be able to uptake them therefore changes in genes and protein expression caused by microRNAs from lipids will not be observed.

This project will help in our understanding of the mechanism of trauma effects transmission. It will also provide potential strategies to prevent transmission of harmful effects to children of individuals who suffer from or stressful conditions.