The role of translational dysregulation in sensory neurons in mediating tactile hypersensitivity in neurodevelopmental disorders (TRANSMECH)

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Approximately 95% of people diagnosed with Autism Spectrum Disorder (ASD) have difficulty processing everyday sensory information, while 60% display altered touch sensation, which can have a profound effect on a person's life. During development, gentle touch communication between mother and infant is essential for proper development of complex behaviours, such as social interaction. Over-sensitivity to touch is observed both in ASD patients and in engineered mouse models carrying mutations of genes linked to ASD. It is plausible that over-sensitivity to touch in ASD patients may be linked to behavioural alterations such as deficits in social interaction. We do not fully understand the mechanisms that account for touch over-sensitivity in ASD. While the precise causes of ASD are unknown, it is established that several risk genes are associated with this disorder. A molecular/cellular pathway that is linked to these ASD risk genes and is commonly affected in ASD patients is involved in regulation of protein synthesis via mTORC1/4E-BP1. We found that selective activation of mTORC1/4E-BP1 only in sensory neurons in mice induced increased synthesis of proteins linked to mitochondria, the cell's powerhouses, which have a central role in energy metabolism. Thus, we hypothesise that the mTORC1/4E-BP1 pathway may be responsible for touch oversensitivity in neurodevelopmental disorders, such as ASD, by favouring the synthesis of certain proteins over others (e.g. mitochondrial proteins). To test this hypothesis in project TRANSMECH, we will use mouse models and human sensory neurons carrying mutations in risk genes found in ASD patients. Understanding this mechanism will lead to the development of novel therapies for treating touch oversensitivity in ASD and also for reversing the core symptoms of ASD (e.g. social behaviour alterations).