TMTC-type O-mannosyltransferases as potential regulators of cadherin-mediated cell adhesion

The function and development of organized tissues in metazoan organisms depends on the complex mechanisms of cell adhesion. Cadherins are a large family of transmembrane glycoproteins which are major contributors to cell adhesion. Their functions are essential for numerous biological and pathological processes, such as neural development, tumor suppression, and epithelial maintenance. Mutations in cadherins lead to a motley of congenital diseases, from neurological abnormalities to cancer. Cadherins are prominently modified with O-mannose within important functional domains by TMTC-type O-mannosyltransferases, however, the in vivo function of these modifications remains poorly understood. Notably, TMTC mutations were found to be associated with brain malformations and neurological disorders, including Cobblestone lissencephaly, a severe congenital disorder characterized by defects in neuronal migration, which reveals that TMTC glycosyltransferases play important roles in nervous system development, possibly by affecting the function of neural cadherins. Defects in the O-mannosylation profile of E-cadherin, caused by a loss of TMTC3 activity was found to decrease cell adhesion in vitro, however, the effect of TMTC mutations on cadherin functions has not been characterized in vivo. TMTCs are well conserved in metazoan organisms, which provides the opportunity to study their functions using experimentally amenable model organisms such as Drosophila. Our analyses of Drosophila TMTC1-3 mutants indicated that these genes function in the nervous system development and are required for axon development in a partially redundant manner. Our initial experiments indicated that these mutants show abnormalities in axon wiring and connectivity, disturbed morphology of axonal tracts, and defects in the patterning of the visual system. Unraveling the relationship between TMTCs and cadherin functions in Drosophila is expected to elucidate evolutionarily conserved functions of TMTCs in mammalian organisms, including humans. Our results may shed light on the pathomechanisms of human disorders associated with defects in the O-mannosylation of cadherins.