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Modeling human intellectual disability and autism: role of the chromatin regulator Setd5 during zebrafish brain development

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SETD5 loss-of-function (LoF) mutations in humans have been recently associated to intellectual disability (ID) and autistic spectrum disorders. Interestingly, SETD5 gene encodes for a putative histone H3 methyltransferase highly expressed in the brain and it falls within the critical interval deleted in the 3p25.3 microdeletion syndrome, characterized by ID, microcephaly and congenital heart defects. The aim of this study is to generate and characterize zebrafish models in which *setd5* has been knocked down or knocked out. Antisense morpholino oligonucleotides-mediated targeting of *setd5* in zebrafish embryos determined microcephaly, cardiac edema and reduced locomotor behavior. Compared to embryos injected with a control morpholino, *setd5* LoF brains, despite their reduced size, show an increase of phospho-H3-positive mitotic cells. We are currently evaluating whether phospho-H3 increase in *setd5* morphants could be actually associated with a possible mitotic arrest, responsible of the increased apoptotic rate in developing brain areas. Furthermore, we generated stable setd5 mutant zebrafish lines through Crispr/Cas9 strategy to analyze the effect of setd5 gene knockout on the phenotype of zebrafish larvae. These animal models will be extremely useful to identify the molecular mechanisms underlying SETD5 LoF phenotype. The future perspective is to screen for compounds able to rescue the developmental defects, to identify novel promising drugs exerting therapeutic efficacy on individuals affected by autism and intellectual disability due to SETD5 haploinsufficiency.