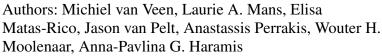
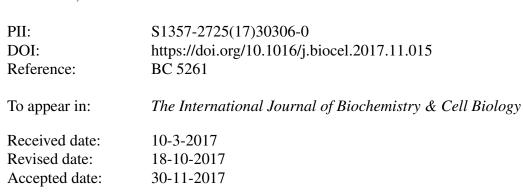
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ACCEPTED MANUSCRIPT

Glycerophosphodiesterase GDE2/GDPD5 affects pancreas differentiation in zebrafish

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Abstract

Notch signaling plays an essential role in the proliferation, differentiation and cell fate determination of various tissues, including the developing pancreas. One regulator of the Notch pathway is GDE2 (or GDPD5), a transmembrane ecto-phosphodiesterase that cleaves GPI-anchored proteins at the plasma membrane, including a Notch ligand regulator. Here we report that Gdpd5-knockdown in zebrafish embryos leads to developmental defects, particularly, impaired motility and reduced pancreas differentiation, as shown by decreased expression of insulin and other pancreatic markers. Exogenous expression of human GDE2, but not catalytically dead GDE2, similarly leads to developmental defects. Human GDE2 restores insulin expression in Gdpd5a-depleted zebrafish embryos. Importantly, zebrafish Gdpd5 orthologues localize to the plasma membrane where they show catalytic activity against GPI-anchored GPC6. Thus, our data reveal functional conservation between zebrafish Gdpd5 and human GDE2, and suggest that strict regulation of GDE2 expression and catalytic activity is critical for correct embryonic

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