The influence of sialylation on cadherin-mediated cell-cell adhesion

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Glycosylation represents one of the most abundant post-translational modifications. Its importance for development is underscored by genetic loss-of-function defects that often lead to early embryonic death. However, the exact reason for this lethality is often unclear. Cell-cell adhesion, which is fundamental to embryo morphogenesis, appears as candidate for being perturbed by glycosylation deficiencies. We thus tried to understand the exact role of glycosylation in cell-cell adhesion during early development using zebrafish as a model system.

In the zebrafish embryo cell-cell adhesion is primarily dependent on adhesion molecules called cadherins. These single transmembrane spanning proteins undergo homo- and heterophilic interactions in which cadherin molecules on apposing cell membranes interact in *trans* to form stable dimers. Additionally, cadherins exhibit clustering in *cis* which cooperates with *trans* binding and strengthens cell-cell contacts. Cadherin glycosylation has been proposed to influence *cis* clustering and thus likely modulates cadherin function.

CMASB is a key enzyme for the transfer of sialic acids onto glycan structures in the zebrafish embryo. Remarkably, downregulation of CMASB resulted in lethal defects in tissue morphogenesis and cellular integrity that recapitulate in many instances known cadherin loss-of-function phenotypes. Impaired *in vitro* sorting of germ layer progenitor cells and disturbed epithelial tissue integrity both indicated reduced cell-cell adhesion due to the loss of CMASB. Finally, direct measurement of cell-cell adhesion by atomic force microscopy shows that this adhesion defect can be linked to E-cadherin function.

We conclude that compromised CMASB-dependent sialylation impairs cadherin function in the zebrafish embryo, resulting in eventually lethal defects in cell-cell adhesion. This would provide a molecular explanation for the essentiality of sialylation in embryonic development.