Tie1 – Angiopoeitin-2 controls Vegf signaling output and links cranial vessel formation with central nervous system development

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Neuro-vascular communication is essential for proper central nervous system development. Here, using the zebrafish model system, we identified the Tie1-Angpt2 signaling axis as a critical regulator of cranial vessel formation and patterning of ependymal cells, the glial cell type responsible for cerebrospinal fluid (CSF) homeostasis in the choroid plexus (CP) of the developing brain. Genetic ablation of Angpt2 impaired vessel lumen remodeling and vessel branching complexity of the mesencephalic vein (MsV), the dorsal longitudinal vein (DLV), and the myelencephalic choroid plexus (mCP). These remodeling defects caused blood flow perfusion deficits at the level of the mCP, culminating into a second wave of remodeling events involving angiogenic sprouts emanating from the mCP, which subsequently connected to the metencephalic artery to establish a collateral network. Genetic ablation of Tie1, phenocopied the cranial vascular defects of Angpt2 mutants, whereas Tie2 and Angpt1 mutants displayed a normal cranial vasculature. Brain specific overexpression of Angpt2 resulted in an expansion of the mCP, with hyperactive endothelial cells displaying supranumerous filopodia extensions. In WT, the distribution of ependymal cells closely associated with the DLV and mCP. In Angpt2 mutants, this association was lost and ependymal cells were mispatterned and dysmorphogenic which correlated with a decrease in brain ventricular volume. Mechanistically, RNA seq, single RNA seq and qPCR identified a series of molecules and cell-cell interactions repressing Vegf-Kdrl signaling in Angpt2 mutants. Accordingly, introducing a Vegf gain of function scenario into Angpt2 mutants rescued the cranial vascular remodeling deficits. These results suggest a hitherto unknown function of the Tie1 receptor and its ligand Angpt2 in the developing zebrafish nervous system. Tie1-Angpt2 signaling acts as a positive regulator of Vegf signaling output relevant for establishing the DLV and mCP plexus, and thereby the correct patterning of ependymal cells, the major regulator of CSF production and distribution. Tie1-Angpt2 thereby connects cranial vessel development with fluid homeostasis in the nervous system. These observations may have implications for understanding the etiology of neurodegenerative diseases including for example Amyotrophic Lateral Sclerosis.