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Titolo	SOX17 IS A CO-EFFECTOR IN WNT/BETA-CATENIN MEDIATED BLOOD-BRAIN BARRIER DEVELOPMENT AND MAINTENANCE [Tesi di dottorato]
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Sommario	The presence of blood-brain barrier (BBB) at the level of endothelial cells (ECs) that line the capillaries in the brain is a challenge while treating intracranial tumors or many neurological disorders since BBB could block the passage of many solvents or drugs entering from systemic circulation to brain parenchyma. Researchers are trying to understand how BBB is induced during development and maintained in adult life in order to develop new tools to enhance drug delivery across BBB. Many signaling pathway that are active during BBB development are unraveled through mainly reverse genetic approach and gene knock out studies. Wnt/?-catenin signaling well known for its role in organ development, morphogenesis and in cancer causation is also reported to be essential for BBB induction and maintenance in most vertebrates. However many target molecules or effectors of this pathway remain to be identified. Previously we have identified Sox17 a SoxF family transcription factor, as a downstream molecule of Wnt/?-catenin signaling. It plays a key role in arterial differentiation of the vasculature of different organs. We found that Sox17 is also expressed at high levels in brain ECs throughout embryo development and in the adult vasculature. EC-specific gain of

	function of ?-catenin (GOF) increases Sox17 expression in BBB ECs and may induce ectopic expression of Sox17 also in the choroid plexus vasculature that lacks the BBB. We hypothesized therefore that Sox17 might be involved in BBB development and maintenance downstream to the Wnt pathway. In Sox17 null mice we analyzed different functional characteristics of BBB such as permeability control and specific markers expression. The absence of this transcription factor leads to increase in BBB permeability to high molecular weight molecules and marked increase in PLVAP, a protein inversely related to maturation of BBB. We also observed significant reduction in the ?-catenin signaling itself by employing BAT-gal reporter in Sox17 15 null background. In addition, many direct ?-catenin targets like Axin2 and LEF1 were decreased upon Sox17 abrogation. These data suggested that Sox17 is not only a target of ?-catenin signaling but also could maintain steady state, detectable levels of ?-catenin signaling. We could rescue ?-catenin signaling and correct BBB defects by either inhibiting the ?-catenin destruction complex or by employing GOF ?- catenin in Sox17 null background. Our study shows that Sox17 is an important regulator of BBB and it partially acts by sustaining ?-catenin signaling. Sox17 expression and signaling may be important in pathological conditions like intracranial tumors and modulation of its activity could have clinical implications and therapeutic benefits.
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