Congenital hydrocephalus and abnormal subcommissural organ development in Sox3 transgenic mice.

ABSTRACT

Congenital hydrocephalus (CH) is a life-threatening medical condition in which excessive accumulation of CSF leads to ventricular expansion and increased intracranial pressure. Stenosis (blockage) of the Sylvian aqueduct (Aq; the narrow passageway that connects the third and fourth ventricles) is a common form of CH in humans, although the genetic basis of this condition is unknown. Mouse models of CH indicate that Aq stenosis is associated with abnormal development of the subcommissural organ (SCO) a small secretory organ located at the dorsal midline of the caudal diencephalon. Glycoproteins secreted by the SCO generate Reissner's fibre (RF), a thread-like structure that descends into the Aq and is thought to maintain its patency. However, despite the importance of SCO function in CSF homeostasis, the genetic program that controls SCO development is poorly understood. Here, we show that the X-linked transcription factor SOX3 is expressed in the murine SCO throughout its development and in the mature organ. Importantly, overexpression of Sox3 in the dorsal diencephalic midline of transgenic mice induces CH via a dose-dependent mechanism. Histological, gene expression and cellular proliferation studies indicate that Sox3 overexpression disrupts the development of the SCO primordium through inhibition of diencephalic roof plate identity without inducing programmed cell death. This study provides further evidence that SCO function is essential for the prevention of hydrocephalus and indicates that overexpression of Sox3 in the dorsal midline alters progenitor cell differentiation in a dose-dependent manner.

Keyword: SOX3; Hydrocephalus; Subcommissural organ.