

A role for inflammation: TLR-4-mediated cerebrospinal fluid hypersecretion in post-hemorrhagic and post-infectious hydrocephalus

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Hydrocephalus is a devastating disease commonly occurring secondary to intraventricular hemorrhage (IVH) or bacterial meningitis. The standard of care, cerebrospinal fluid (CSF) shunting, is an invasive neurosurgical procedure that is prone to complications, requiring multiple revision surgeries, and dramatically decreases quality of life. A fundamental obstacle in developing novel therapeutics for hydrocephalus has been a relative lack in our understanding of the pathophysiology of the choroid plexus epithelium (CPE) following IVH and bacterial meningitis. Recently, our group has demonstrated a novel role of TLR-4-mediated CSF hypersecretion following IVH that causes acute post-hemorrhagic hydrocephalus (PHH). CSF hypersecretion is secondary to an increase in the functional expression of the NF- κ B-regulated Ste20-type stress kinase STK39 (SPAK), binds, phosphorylates, and stimulates the ion co-transporter, NKCC1 (critical for CSF secretion) at the apical CPE membrane. Strikingly, PHH could be attenuated by genetic and pharmacological manipulation of TLR-4, NF- κ B, SPAK or NKCC1. Interestingly, post-infectious hydrocephalus (PIH) exhibits non-obstructive ventriculomegaly, CPE inflammation, and a positive response to endoscopic choroid plexus cauterization. Lipopolysaccharide (LPS), the canonical TLR-4 ligand, is a component of many PIH-causing bacteria. Here, we begin to show that

PHH/PIH may share a common pathogenic mechanism of TLR4-dependent CSF hypersecretion and acute hydrocephalus via a similar up-regulation of TLR-4-regulated ion transporters in the inflamed CPe. We propose instead of being classified as "secondary" forms of hydrocephalus, PHH/PIH may be better termed "inflammatory hydrocephalus" to highlight overlapping disease mechanisms and potential therapeutic vulnerabilities