Bone morphogenetic protein signaling: a promising target for white matter protection in perinatal brain injury

Prematurely born newborns, as well those born at term, may suffer from several types of brain injury including hypoxic-ischemic injury, intraventricular hemorrhage, and parenchymal, and injury that is the consequence of intrauterine growth restriction (IUGR). Injury of all types can impact the motor and cognitive abilities of survivors. The mechanisms leading to disability are not completely understood. Here we discuss the role of the bone morphogenetic protein (BMP) signaling pathway in newborn brain injury. We review the evidence that the BMP signaling pathway is activated in various injury types and discuss the downstream effects of its activation and possible interventions to curtail the effects of this pathway’s activation. In addition, we identify interactions with other signaling pathways important in neurodevelopment.

Perinatal brain injury: The newborn period is a time of risk for neurologic injury. Newborns born at the limits of viability are at particularly high risk. In a recent study, survivors born at 23 weeks gestation had only a 17.9% rate of survival without severe neurodevelopmental impairment (NDI). Severe NDI was defined as a cognitive or motor score on the Bayley Scales of Infant and Toddler Development (Bayley III) greater than 2 standard deviations below the mean, a Gross Motor Function Classification System (GMFCS) level of 4 or 5, or bilateral blindness or deafness not corrected by bilateral amplification (Rysavy et al., 2015). For preterm newborns born at term, NDI is often associated with birth asphyxia or hypoxic-ischemic encephalopathy (HIE). At term, the incidence of HIE in the developed world is 1–3 per 1000 live births. Risk factors for HIE include abnormal cardiotocography, prolonged membrane rupture, thick meconium, shoulder dystocia, tight nuchal cord, sentinel events and failed vacuum delivery. The rate of death or moderate to severe brain injury following HIE ranges from 44% to 62%, depending on whether the infant received therapeutic hypothermia, with severe NDI defined similarly as for preterms except for the use of the Bayley II, a GMFCS level of 3 to 5, and deafness that can be corrected by amplification (Natarajan et al., 2014). Another clinical entity seen at term and near-term gestation is arterial ischemic stroke, which has an incidence of between 1 in 2300 to 5000 live births. Long term sequelae of arterial ischemic stroke includes cerebral palsy, attention problems, behavioral problems, speech and language delay and epilepsy (Lehman and Rivkin, 2014). There is emerging evidence that perinatal risk factors such as IUGR also result in long-term impairment in cognitive, language, and motor development in both preterm and term infants compared to their age matched counterparts. IUGR is defined as a significant reduction in fetal growth rate resulting in birth weight < 10th percentile for gestational age and is estimated to occur in 5% to 7% of all pregnancies. The most common identifiable cause of IUGR is uteroplacental insufficiency. Population-based cohort studies have shown significant motor delays and as much as a 5–7 fold increased risk of developing cerebral palsy in growth restricted term infants (Levine et al., 2015). Thus newborns, both preterm and term, are a patient population particularly burdened by brain injury. For this reason, there is a high interest in developing therapeutic interventions for this patient population that will preserve as much cognitive and/or motor function as possible.

BMPs in neurodevelopment: Injury during the newborn period is unique in that it occurs during critical stages of brain development. The brain continues to develop postnatally and the normal newborn period presents a time of intense myelination of neurons. In preterms, the brain is in even earlier stages of development. It is important to note here that the newborn period represents a time when myelination normally occurs. BMPs are often associated with intraventricular hemorrhage and parenchymal, and injury that is the consequence of intrauterine growth restriction (IUGR). Injury of all types can impact the motor and cognitive abilities of survivors. The mechanisms leading to disability are not completely understood. Here we discuss the role of the bone morphogenetic protein (BMP) signaling pathway in newborn brain injury. We review the evidence that the BMP signaling pathway is activated in various injury types and discuss the downstream effects of its activation and possible interventions to curtail the effects of this pathway’s activation. In addition, we identify interactions with other signaling pathways important in neurodevelopment.

Evidence for changes in BMP signaling in perinatal brain injury: The preponderance of evidence for changes in BMP signaling in brain injury derives from the adult stroke literature. Yet BMP signaling in perinatal brain injury has been minimally studied. Given especially the adult stroke findings, it is logical to examine BMP signaling in perinatal brain injury.

Perinatal hypoxia-ischemia: Although focal stroke is observed in the neonate, global hypoxia-ischemia (HI) is more frequently observed, and this type of injury has been the focus of our lab. Because loss of white matter and mature oligodendrocytes (OLs) following HI and blocked differentiation of oligodendroglial progenitor cells (OPCs) following recurrent HI have been observed, we have specifically investigated the role of BMP in oligodendroglial differentiation. We have shown that BMP4 expression is downregulated in the downstream effect of canonical BMP signaling, SMAD1/5/8, is increased following global perinatal HI using the Vannucci injury model in which postnatal day 7 mice are subjected to common carotid artery ligation then 8% hypoxia for 60 minutes. Given that BMPs negatively regulate the differentiation of neural stem cells into oligodendrocytes, we hypothesized that downregulation of BMP signaling would result in oligodendrocytes. We first tested this hypothesis using a noggin-overexpressing transgenic mouse engineered to express noggin after completion of neuronal differentiation by driving expression from the NSE promoter (NSE-noggin) and found an increase in OPCs and OLs 7 days post injury in injured NSE-noggin mice compared to injured wild type (WT) mice. In addition, we found an improvement in ambulation 14 days post injury in NSE-noggin mice compared to injured WT mice (Dizon et al., 2011). Using this strategy, it was not possible to attribute outcomes to changes in BMP signaling within oligodendroglia exclusively; outcomes could potentially be caused by changes in signaling within neurons or astrocytes alone or in combination with oligodendrocytes. In addition, noggin overexpress-
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Intraventricular hemorrhage: BMPs were shown to be upregulated in a model of intraventricular hemorrhage induced by intraperitoneal glycerol in rabbits. Inhibition of BMP signaling resulted in functional recovery following IVH. In this model, IVH was associated with hypomyelination and gliosis. Moreover, inhibition of BMP signaling following IVH using recombinant human noggin resulted in normalization of SMAD 1/5/8, rescue of OLs and myelin and recovery of motor function recovery (Dummula et al., 2011). There are currently no studies examining BMP signaling in perinatal non-IVH intracranial hemorrhage or stroke, however BMP signaling has been studied extensively in adult stroke.

Intrauterine growth restriction: Recent studies have shown that a significant factor in the pathogenesis of the NDI seen with IUGR is white matter injury characterized by damage to OLs, impaired myelination and astrogliosis. Major consequences of IUGR on uteroplacental insufficiency include chronic hypoxia and induction of oxidative stress, which has been shown to inhibit oligodendroglial differentiation. Elevated BMP4 has been demonstrated in a rat model of IUGR created by bilateral ligation of the uterine artery. Moreover, it has been demonstrated that OPCs cultured postnatally from this model retained increased BMP expression and impaired differentiation that was reversed with the BMP inhibitor noggin (Reid et al., 2012). Our laboratory utilizes a novel in vivo model of IUGR that mimics preeclampsia, the most common cause of uteroplacental insufficiency and IUGR in developed countries, using a thromboxane A2 analog (Fung et al., 2011). We are currently testing if oligodendroglial and white matter loss and motor deficits occur in this model and if BMP signaling is involved.

Blood-brain barrier (BBB) permeability and BMP signaling: Intriguingly, increased signaling through BMP receptors in OPCs after brain injury may be stimulated by non-BMP ligands and by blood-derived signals. Peterson et al. (2017) found that the blood-derived coagulation factor fibrinogen deposits in the brain following BBB disruption, activating the BMP signaling pathway in OPCs and suppressing remyelination. Fibrinogen activated the phosphorylation of Smad 1/5/8, altered the Akt and mTOR signaling pathways and inhibited astrocyte maturation and gliosis. Together our data suggests that increased BMP signaling associated with perinatal HI negatively impacts the survival of OPCs and OLs and suppresses the production of proteins important in myelination.

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