The limited ability of the central nervous system (CNS) to regenerate in adult mammals after injury or disease is a significant problem. Intriguingly, neural stem/progenitor cells (NSPCs) offer hope for repairing the CNS. Endogenous or transplanted NSPCs contribute to repair processes, but their differentiation and function are abnormal in CNS injury and disease. The main reasons for these abnormalities are changes in the extracellular environment in the injured CNS that alter pathways and transcriptional regulation in NSPCs. In CNS disease with vascular permeability or blood-brain barrier disruption, blood-derived fibrinogen enters the parenchyma and drastically changes the extracellular environment of brain cells, including NSPCs. Fibrinogen is present in the brain in a wide range of CNS pathologies, such as multiple sclerosis, Alzheimer’s, Parkinson’s, and traumatic brain injury. Here, within this perspective, we focus on how the blood-derived coagulation factor fibrinogen alters the subventricular zone (SVZ) stem cell niche environment to activate the bone morphogenetic protein (BMP) receptor (BMPR) signaling pathway in NSPCs. The activated BMPR signal increases p75 neurotrophin receptor (p75NTR) and inhibitor of DNA binding 3 (Id3) abundance in NSPCs, and thus, regulates NSPC migration and differentiation in a mouse model of cerebral infarction (photosensitization and ischemia) and cortical brain trauma (stab wound injury) (Pous et al., 2020; Deshpande et al., 2021). NSPCs located in the adult SVZ are a potential source for cell replacement and brain repair. The fine-tuned cellular and molecular niche environment controls the cardinal features of the SVZ: NSPCs: an unlimited capacity for self-renewal, indefinite ability to proliferate, and multipotency for the different neuroectodermal lineages of the CNS. Pathological states induce dynamic changes in NSPCs, but the regulatory mechanisms that control NSPC differentiation in CNS disease are largely unknown. In contrast to the human brain SVZ, where progenitor enclaves are highly recruted by 2 years of age and little to no neurogenesis is observed after childhood, the adult rodent brain still produces neurons during neurodevelopment. This SVZ neurogenesis is necessary for migration and differentiation in a mouse model of cerebral infarction (photosensitization and ischemia) and cortical brain trauma (stab wound injury) (Pous et al., 2020; Deshpande et al., 2021). By enhancing BMPR type I association in lipid rafts through its αc domain-B1 integrin binding, fibrinogen enhances BMP signaling in a ligand-independent manner and directs lineage specification of SVZ NSPCs into newborn astrocytes (Pous et al., 2020). Furthermore, increased levels of BMPR-signaling induces SVZ-derived NSPCs and their progeny to expand their migration area (Deshpande et al., 2021). BMPR signaling regulates the levels of p75NTR and genetic depletion of p75NTR in SVZ NSPCs results in reduced migration towards the lesion area after cortical injury. p75NTR, a member of the tumor necrosis factor receptor superfamily, participates in multiple intracellular signaling pathways involved in the range of biological functions that promote or inhibit the overall process of tissue repair (Malik et al., 2021). Increased p75NTR expression results in cytoskeletal remodeling and organogenesis necessary for NSPC migration and orchestrates the SVZ NSPCs to sense the brain-derived neurotrophic factor radiant in the lesion area and to redirect their migration path towards the cortical lesion area. BMPR is found in the cytoplasm of Rho GTPase activating and inhibiting proteins in adult SVZ NSPCs. Rho family proteins are active in response to extracellular signals, including soluble cytokines, growth factors, and neurotrophins. Full-length p75NTR in SVZ NSPCs may be a sensor for increased cortical lesion size-brain-derived neurotrophic factor gradients to modulate Rho family activity and facilitate the SVZ-originating astrogenic response in CNS disease. Yet, the underlying mechanisms of how p75NTR regulates Rho GTPase activating and inhibiting proteins and the cytoskeletal rearrangements in NSPCs remain to be an attractive research topic. We suggest that BMP-induced p75NTR abundance regulates the migration of SVZ-derived NSPCs and their contributions to regeneration at injury sites (Deshpande et al., 2021). Overall, our data revealed that early and robust changes of the stem cell niche environment with deposition of the provisional fibrin matrix alter the magnitude of BMPR signaling and orchestrates an SVZ-originating astrogenic response contributing to the regeneration process in CNS disease.

Linking environmental changes with NSPC function: The Id transcriptional regulator: Reprogramming NSPCs' origin and functionality by modulating transcription is a promising way to promote CNS regeneration. However, the transcriptional network that regulates those activities under pathological conditions is only poorly understood. Pioneering studies identified the basic helix-loop-helix (bHLH) transcription factor (TF) Olig2 as a suppressor of neuronal lineage. Antagonizing Olig2 function in vivo resulted in a significant number of immature neurons (Buffo et al., 2005). Ecotopic expression of Olig2 in adult rat embryos that were kept in the spinal cord, led to efficient production of oligodendrocytes enabling spinal cord repair (Ulloa-Borboa et al., 2019). We support the concept that targeting the bHLH TF protein family might be an attractive avenue for harnessing endogenous NSPCs for repair.

Inhibitors of DNA binding proteins function as dominant-negative regulator of bHLH TFs and are critical players that control stem cell function (Chu et al., 2021). Our results showed that early and robust changes to the stem cell niche environment trigger Id expression in NSPCs and orchestrate the SVZ-originating astrogenic response. Specifically, we found that BMPR-signaling-induced Id3 expression in the stem cell niche promotes NSPC differentiation into astrocytes by restraining the transcriptional activity of the bHLH TF E47 (Bohrer et al., 2015; Pous et al., 2020). In addition to astrocyte-specific genes (e.g., glutamatergic acid aspartate transporter, known as Slc38a3), the Id3-E47 axis regulates several solute carrier (SLC) family members (e.g., Slc1a2, Slc5a2, Slc3a1, Slc9a14, Slc9a11), suggesting a potential role of Id3 in the regulation of SLC homeostasis and metabolism upon environmental changes. The functional diversity of each Id member under different diseases remains to be investigated, but will probably be derived from their conformational flexibility and preference to interact with divergent binding partners. Yet, the power of Id proteins to orchestrate altered environmental cues into changes of a repertoire of gene expression and cellular activity implies a potential of cell- and/or disease-dependent modification of specific biological pathways in therapeutic intervention (Chu et al., 2021). Interestingly, blood-derived fibrinogen activates BMP signaling in oligodendrogenic progenitor cells, inhibiting oligodendrogenesis in multiple sclerosis (Peterson et al., 2017). While Id3 upregulation in NSPCs induces astrogenesis (Bohrer et al., 2015; Pous et al., 2020), Id2 upregulation in oligodendrocyte progenitor cells might inhibit oligodendrogenesis differentiation (Chu et al., 2021).

Overall, our findings show that early and robust changes of the stem cell niche environment with deposition of the provisional fibrin matrix alter the magnitude of BMPR signaling orchestrating a transcriptional network that mediates the SVZ-originating regenerative response in CNS disease.
adult mammalian SVZ stem cell niche is a primary site of vulnerability to CNS injury and disease and that fibrinogen is rapidly deposited in the SVZ when stem cell niche environment and alters the NSPC behavior (Figure 1). Fibrinogen's pleiotropic roles (e.g., activating CNS inflammation, inducing scar formation, and modulating neural stem cell behavior) play a key role in the neops of gliogenesis, immunity, and regeneration processes at the brain-vascular interface. Fibrinogen-regulated NSPC-derived astrogliosis from the SVZ niche might have unique beneficial effects in the lesion area, such as contribution to 'glial scar formation' and 'cell replacement' as well as 'neuroprotection' and 'immunomodulation', which overall promote the repair process. On the other hand, misregulated fibrinogen deposition in the stem cell niche might be a sensitive indicator for detrimental effects and potential initiation of CNS disease. Microglia are early responders to the altered environment, and the SVZ niche is susceptible to T-cell infiltration in aged mice and humans (Dullen et al., 2019). Early changes of the SVZ niche environment might lead to changes in SVZ niche cells, e.g., microglia and ependymal cells that affect the CSF composition and long-range communication, such as reducing endothelial barrier properties and inflammation (Figure 1). In addition, misguided BMP signaling triggered by excess fibrinogen deposition in the SVZ leads to id and p75 expression. Misregulation of Id family members and p75 are connected to the self- renewal capacity, as well as migration capacity of NSPCs and tumor invasion, respectively (Johnston et al., 2007; Lee et al., 2016). SVZ NSPCs are suspected to be the origin of glioblastoma (Lee et al., 2018), and misregulated id or p75 expression due to an altered SVZ environment might contribute to glioblastoma formation (Figure 1). However, the cell population of origin for glioblastoma and the contribution of an altered extracellular environment besides genetic alterations are still under debate and will be the content of future reviews. Overall, these observations suggest several interesting research questions: How do early environmental changes in the SVZ affect local SVZ cell-cell communications, such as reciprocal interaction between SVZ NSPCs and microglia? Does the altered SVZ cell-cell communication contribute to peripheral immune cell infiltration and disease initiation? Can we apply our knowledge about identified molecular pathways involved in the differentiation of resident adult brain SVZ NSPCs to control fate and functions of transplantable NSPCs tailored to promote CNS repair and humans? (Figure 1)

Future studies will shed light on the mechanisms of how a vulnerable SVZ stem cell niche instructs NSPC behavior and local and long-range communication and how these mechanisms might be harnessed to promote CNS repair.

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Figure 1 The SVZ is a vulnerable site in CNS disease.

CNS injury and disease results in increased SVZ vasculature permeability and fibrinogen deposition into the SVZ stem cell niche environment. The deposition of fibrinogen activates BMPR-1 signaling and induces phosphorylation of Smad1/5/8 by BMP signaling in NSPCs, inducing astroglialization and migration of SVZ NSPCs towards the lesion site. BMPR-1: Bone morphogenetic protein receptor; CB: cerebellum; CNS: central nervous system; CSF: cerebrospinal fluid; DG: dentate gyrus; Id3: inhibitor of DNA binding 3; LV: lateral ventricle; NSPCs: neural stem/precursor cells; NTR: neurotrophin receptor; OB: olfactory bulb; RMS: rostral migratory stream; SVZ: subventricular zone.

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