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PATHWAYS & KEY MOLECULAR TARGETS

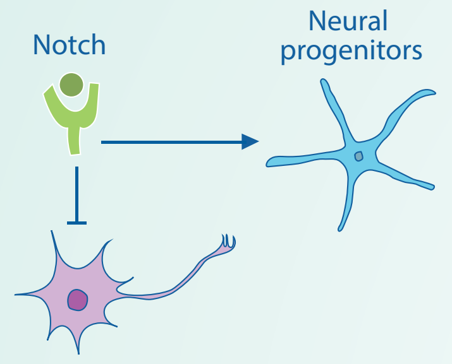
Astrocyte Development & Function

Contributors: Debosmita Sardar, PhD., Yi-Ting Cheng, MS., Benjamin Deneen, PhD., Baylor College of Medicine, Houston, TX 77030 (e-Mail: deneen@bcm.edu)

Astrocyte Development

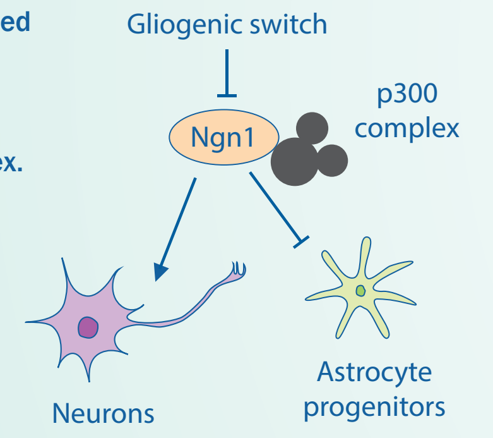
Maintenance of neural stem cells

Notch maintains the neural progenitor cell pool through HES1/5, which suppresses neurogenesis by inhibiting the bHLH transcription factor Ngn1/2.



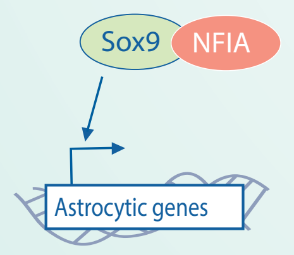
Suppression of neurogenesis

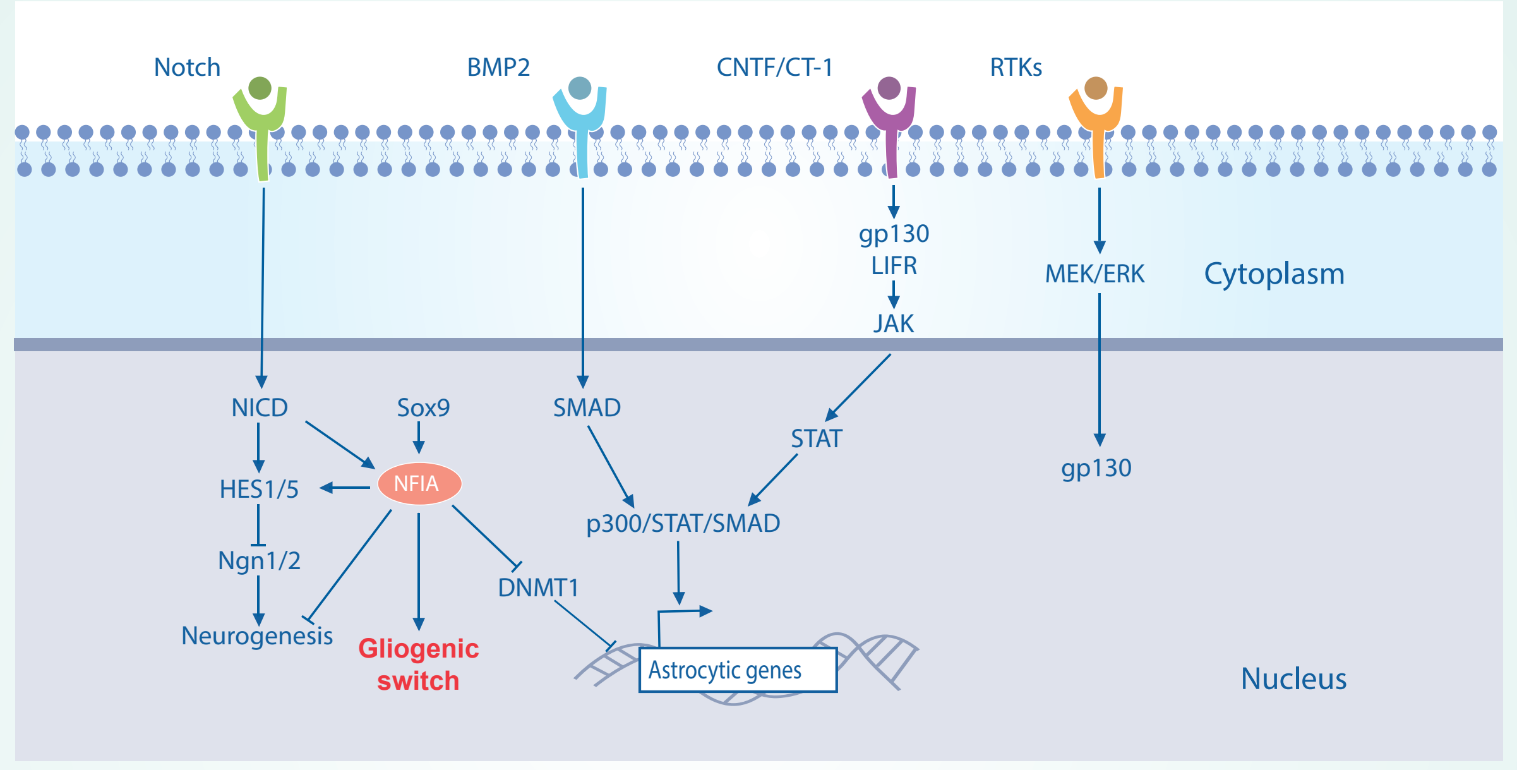
The gliogenic switch is controlled by the downregulation of neurogenic factors. Ngn1 suppresses gliogenesis by sequestering the p300 complex. Additionally, gliogenesis is promoted by the downregulation of Coup TFI/II and ErbB4, which suppresses neurogenesis.

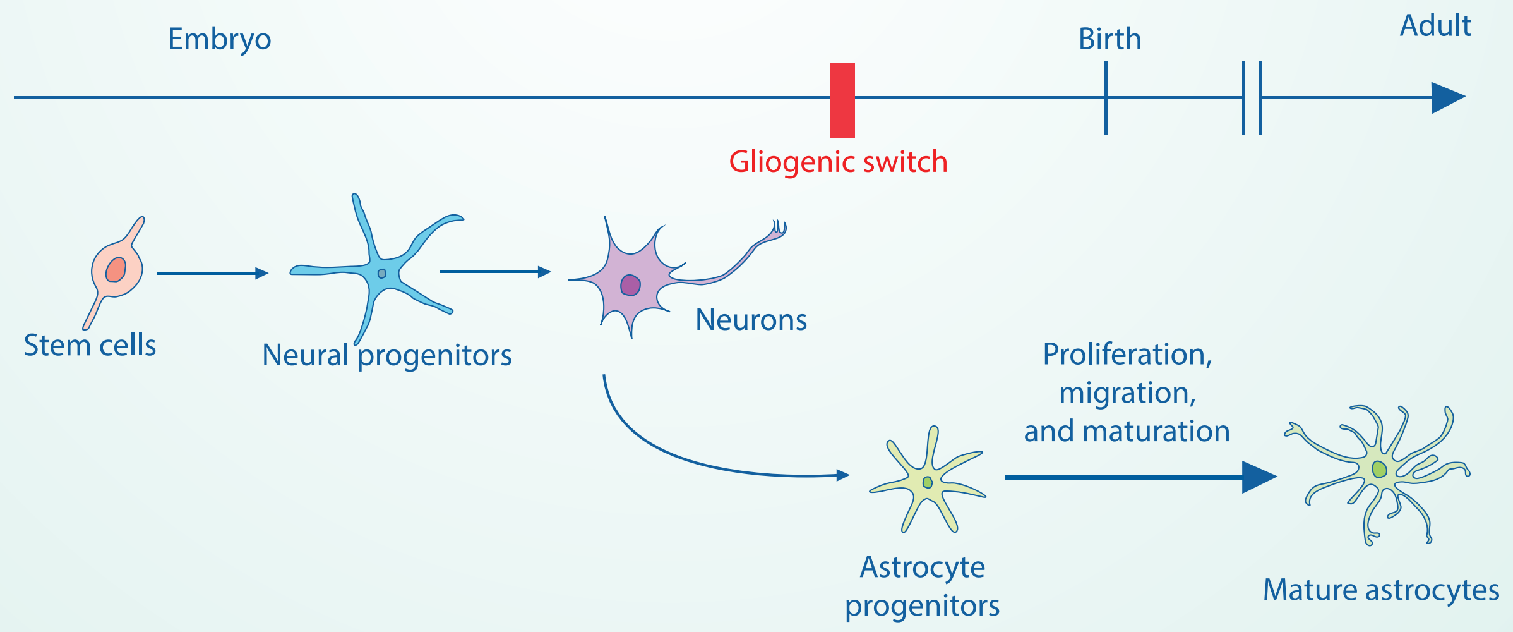


Transcriptional control in the gliogenic phase

Following initiation of gliogenesis, NFIA and Sox9 cooperate to regulate genes involved in astrocyte differentiation. In contrast to our knowledge of gliogenic switch drivers, less is known about the transcriptional control of astrocyte migration, proliferation and transformation into mature cells that are capable of carrying out complex biological functions.

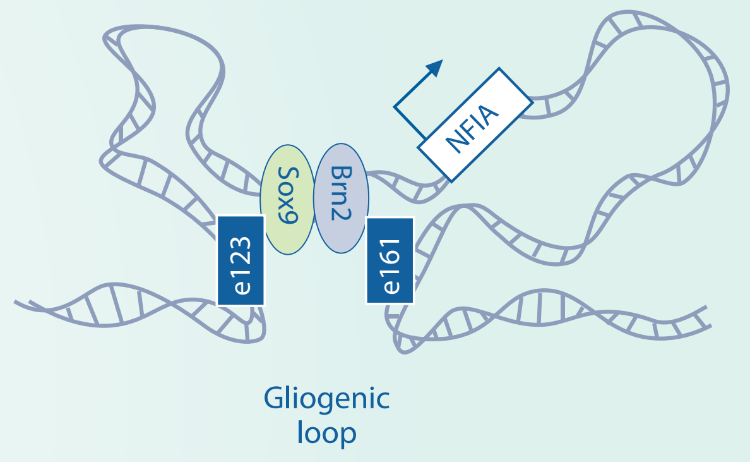






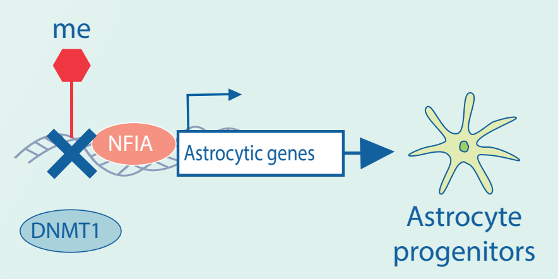
Role of chromatin architecture

Long-range interactions between specific enhancer regions and the NFIA promoter form distinct chromatin loops, termed the 'gliogenic loop', which lead to the induction of NFIA and the switch to gliogenesis.

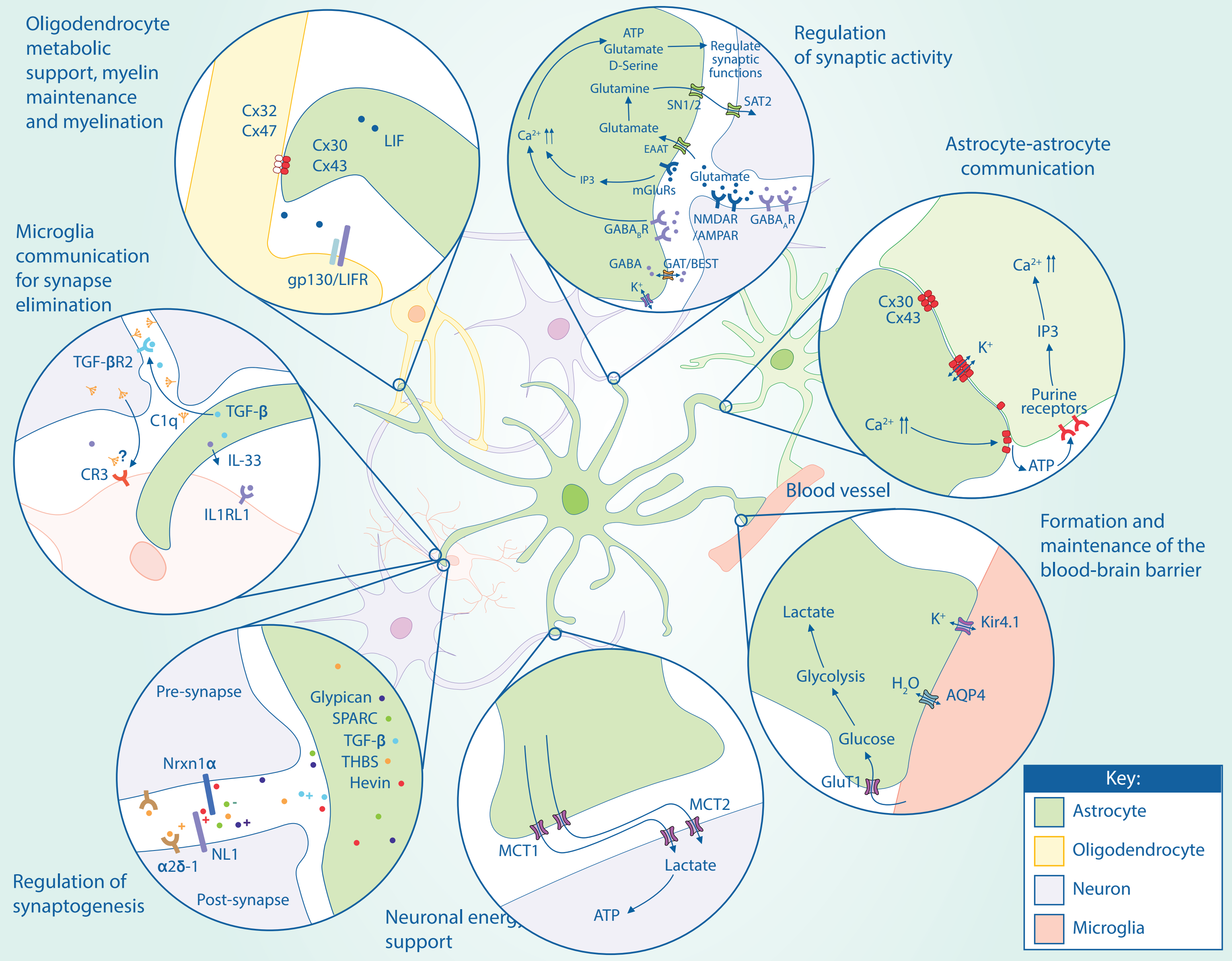


Epigenetic control

Loss of DNA methylation at astrocytic gene promoters is necessary for progenitors to differentiate. One mechanism driving this process is displacement of DNMT1 from astrocytic gene promoters, facilitated by binding of NFIA at these promoters.



Astrocyte Functions in CNS



Legends

1. Astrocyte Development
Neural progenitors undergo neurogenesis first, after which there is a gliogenic switch to the formation of astrocytes. Transcription factor NFIA is crucial for the gliogenic switch and astrocyte fate specification. Concomitant suppression of neurogenesis is necessary for this fate specification. Expression of Hes1/5 is maintained by NFIA to further suppress neurogenesis. After fate determination, astrocyte precursors undergo differentiation controlled by the concerted actions of JAK-STAT and SMAD pathways. Recently, the MEK/ERK pathway has also been shown to be involved by inducing the expression of a cytokine receptor, gp130. In addition, the competency of astrocytic promoters needs to be in a permissive state for astrocyte differentiation. Demethylation of the STAT binding site by NFIA displacement of the methyltransferase DNMT1 facilitates this process. Furthermore, a specific chromatin conformation has been recently shown to dictate the gliogenic switch. Following glial fate specification and differentiation, astrocytes mature into complex functional entities. The next big question lies in delineating the transcriptional control of how the complex biology of astrocyte maturation unfolds.

2. Astrocyte Functions in CNS
Mature astrocytes take part in a variety of functions essential for the operation of the CNS. Astrocytes are important in synapse formation and regulation of synaptic activity, where they work by forming tripartite synapses. Apart from communicating with neurons, astrocytes also communicate with each other through gap junctions, modulate the blood-brain barrier, maintain energy homeostasis, and interact with other cell types of the CNS such as oligodendrocytes and microglia.

3. Astrocyte Diversity
Although astrocyte diversity was first observed more than 50 years ago, it was only recently that scientists started to explore the diversity of astrocytes again. An unresolved question is the role of patterning during development in the regional diversity of astrocytes. A number of studies have shown that astrocytes exhibit regional diversity both in brain and spinal cord. However, it is still unclear how regional diversity links to functional diversity and which molecular mechanisms control this process.

4. Role of Astrocytes in Disease and Injury
Astrocytes in diseased states can be classified into two types. First, dysfunctional astrocytes are observed in neurodevelopmental diseases and in brain cancer. Second, neurodegenerative diseases and injury transform healthy astrocytes to reactive ones. Reactive astrocytes function to initially protect the CNS from diseased states, but eventually proceed to have detrimental effects leading to disease progression.

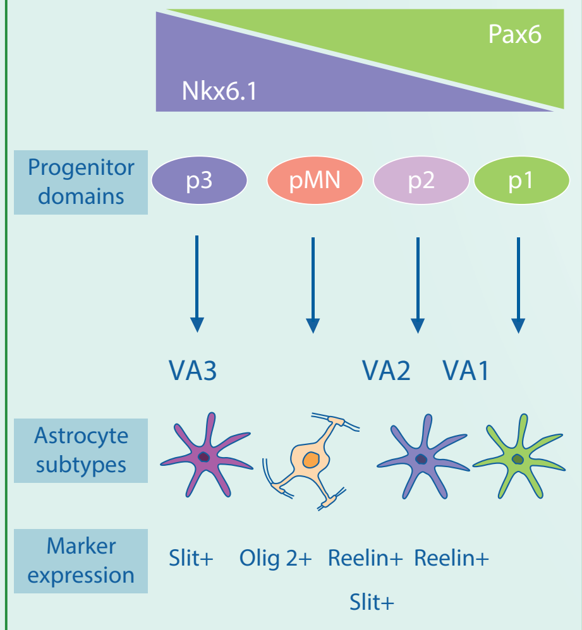
Astrocyte Diversity

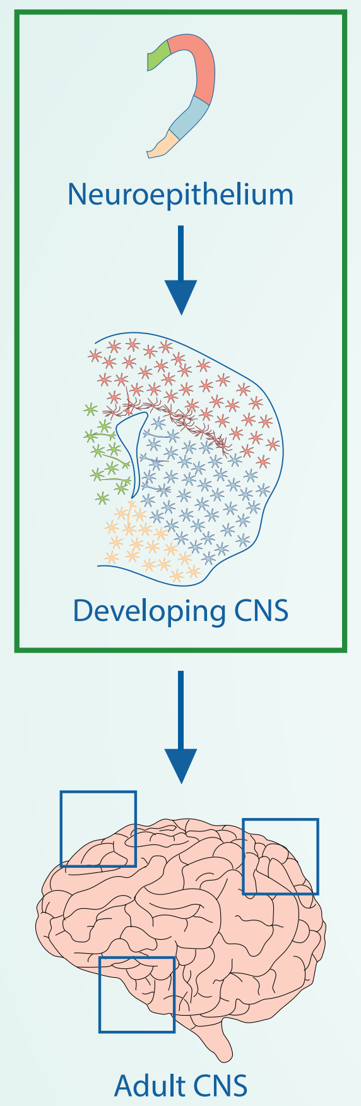
Regional diversity arising from precursor migration

The Rowitch Lab (Tsai *et al.* Science, 2012) fate-mapped astrocytes throughout the brain and spinal cord to show that astrocytes are regionally allocated in domains based on their original location at the ventricular zone. Specific domain architectures were maintained even after injury.

Regional diversity arising from developmental patterning

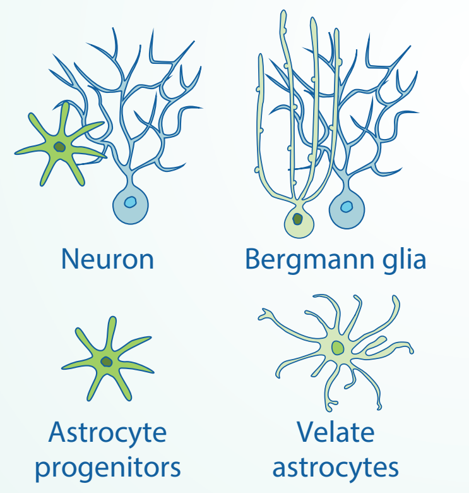
The Anderson Lab (Hochstim *et al.* Cell, 2008) showed that white matter astrocyte diversity is positionally dependent on the unique expression pattern of transcription factors along the dorsoventral axis of the spinal cord.





Local microenvironment affects astrocyte diversity

In the cerebellum, local signaling mediated by neuron derived Shh, controls the sub-type distinction of astrocytes into the Bergmann glia or the velate astrocytes. In addition, astrocytes from different brain regions were shown to respond differentially to neuronal Shh signaling. This demonstrated that neuron-astrocyte communication in local microenvironments regulates astrocyte diversity (Farmer *et al.* Science, 2016).

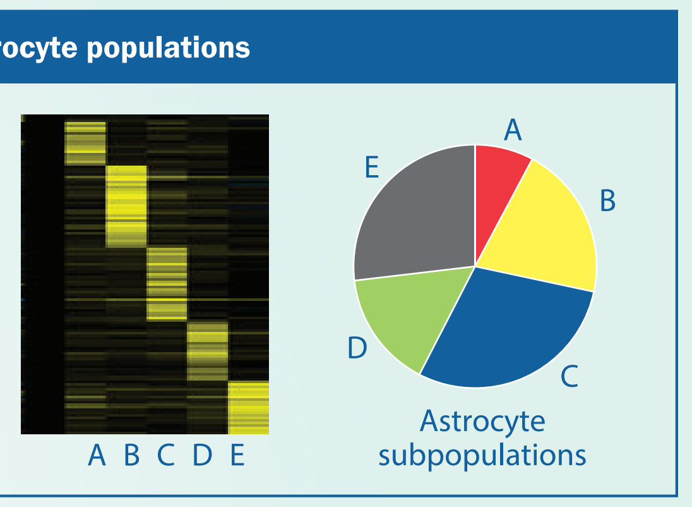


Regionally restricted astrocytes are functionally heterogeneous

Molofsky *et al.* (Nature, 2014) showed that in the postnatal spinal cord, ventral astrocytes secrete semaphorin 3a, which is necessary for circuit organization of subtype-specific motor neurons. Concomitantly, in the dorsal spinal cord, semaphorin 3a repels subtype-specific sensory afferent fibers. This shows that astrocytes' positional codes are necessary for circuit formation of subtype-specific neurons.

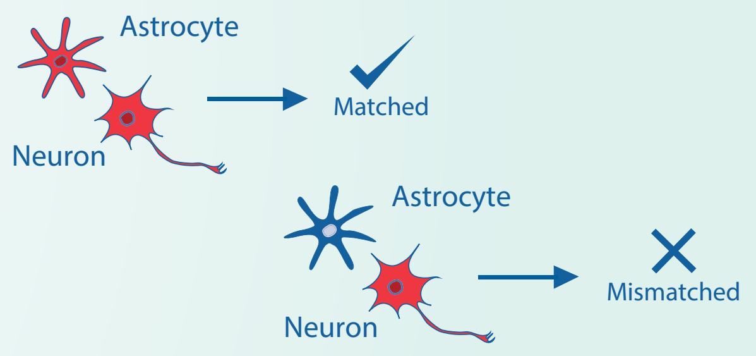
Local astrocyte diversity defined by discovery of distinct astrocyte populations

The Deneen Lab (Lin *et al.* Nat. Neurosci. 2017) resolved local astrocyte diversity across the brain by separating astrocytes based on cell surface markers. This led to the identification of distinct subpopulations at each brain region. These populations are also maintained across the brain in disease states of glioma.



Regional specificity of astrocytes dictates communication with neurons

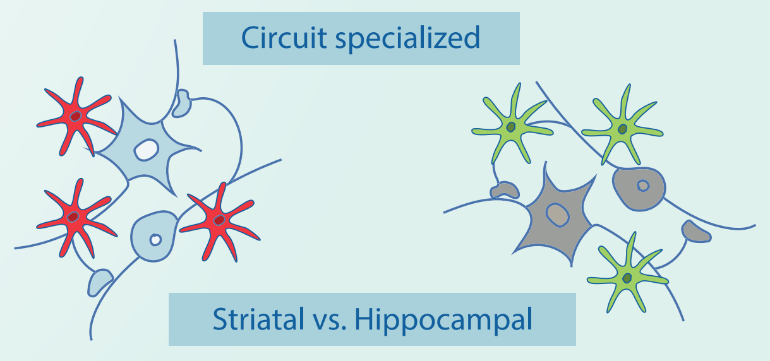
Using *in vitro* mismatched cultures of astrocytes and neurons from different brain regions, Morel *et al.* (J. Neurosci. 2017) showed that astrocytes from one region selectively promote neurite growth and synaptic activity of neurons from the same region, exhibiting region-matched astrocyte neuron communication. Indeed, one of the first examples of region-encoded control by astrocytes was reported in 1984 (Denis-Donini *et al.* Nature) that showed glial cells from different regions control neuron shape.



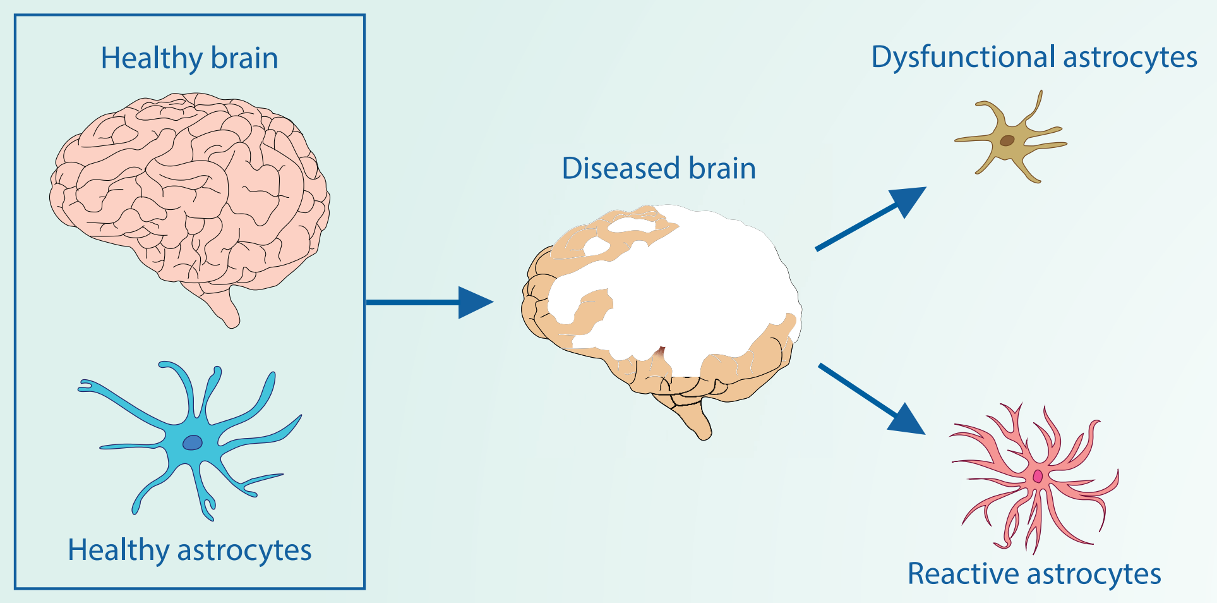
Astrocyte diversity in regionally distinct neural circuits across the brain

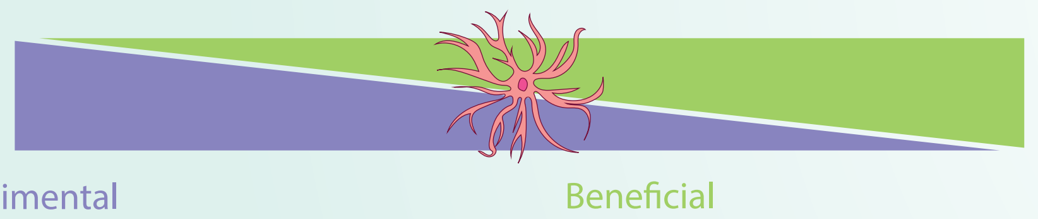
The Khakh Lab (Chai *et al.* Neuron, 2017) explored astrocyte diversity in regionally distinct neural circuits across the brain using multiple integrative approaches. The different populations displayed dissimilarities in:

- Electrophysiology
- Ca^{2+} signaling
- Morphology
- Positioning at synapse



Role of Astrocytes in Disease and Injury





Detrimental
- Secretion of inflammatory factors
- Reduction of axonal plasticity
- Formation of glial scar

Beneficial
- Homeostatic and trophic support
- Blood-brain barrier reconstitution
- Promotion of cell proliferation
- Formation of glial scar

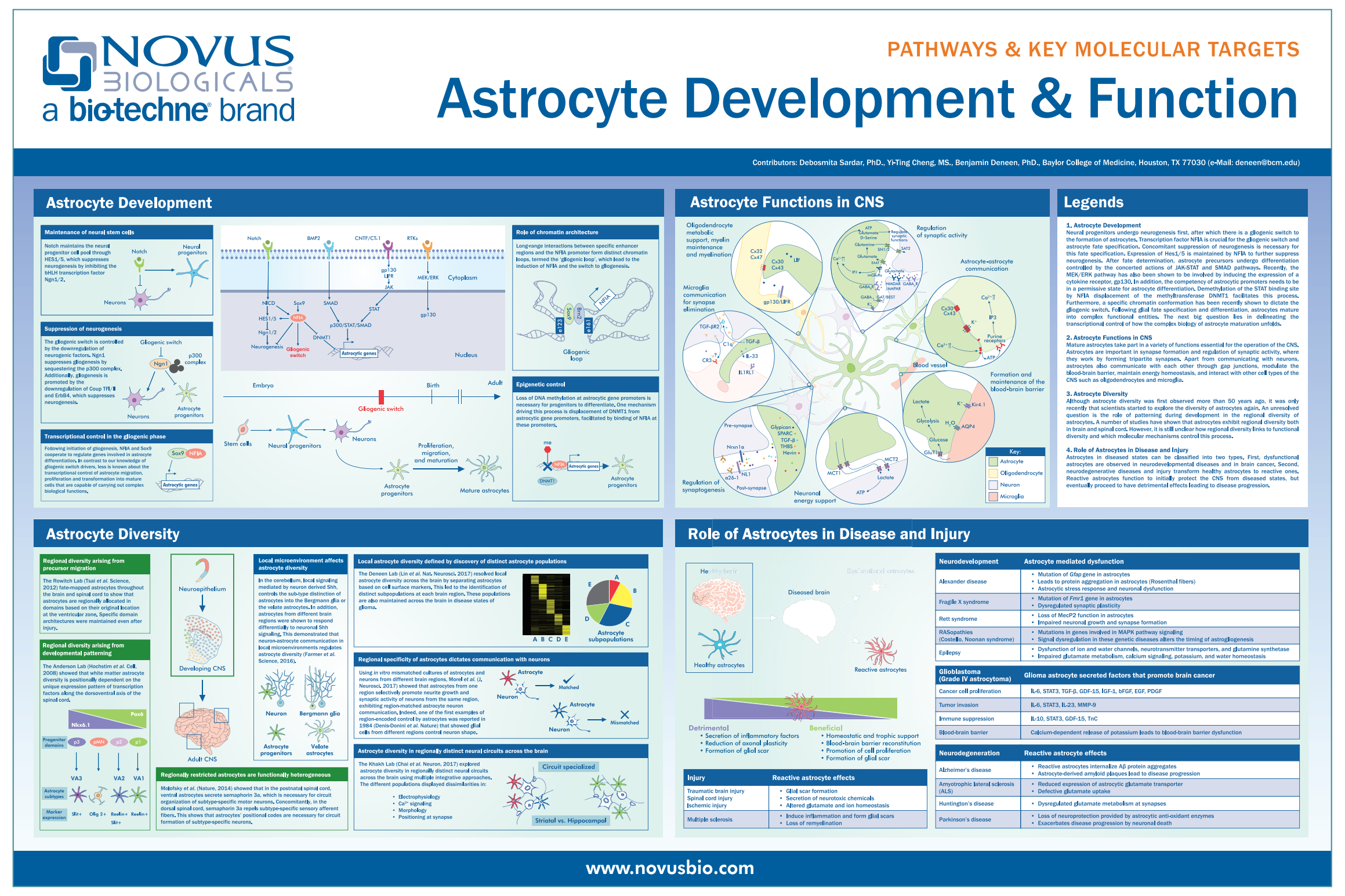
Injury	Reactive astrocyte effects
Traumatic brain injury Spinal cord injury Ischemic injury	• Glial scar formation • Secretion of neurotoxic chemicals • Altered glutamate and ion homeostasis
Multiple sclerosis	• Induce inflammation and form glial scars • Loss of remyelination

Neurodevelopment	Astrocyte mediated dysfunction
Alexander disease	• Mutation of *Gfap* gene in astrocytes • Leads to protein aggregation in astrocytes (Rosenthal fibers) • Astrocytic stress response and neuronal dysfunction
Fragile X syndrome	• Mutation of *Fmr1* gene in astrocytes • Dysregulated synaptic plasticity
Rett syndrome	• Loss of MecP2 function in astrocytes • Impaired neuronal growth and synapse formation
RASopathies (Costello, Noonan syndrome)	• Mutations in genes involved in MAPK pathway signaling • Signal dysregulation in these genetic diseases alters the timing of astrogliogenesis
Epilepsy	• Dysfunction of ion and water channels, neurotransmitter transporters, and glutamine synthetase • Impaired glutamate metabolism, calcium signaling, potassium, and water homeostasis

Glioblastoma (Grade IV astrocytoma)	Glioma astrocyte secreted factors that promote brain cancer
Cancer cell proliferation	IL-6, STAT3, TGF-β, GDF-15, IGF-1, bFGF, EGF, PDGF
Tumor invasion	IL-6, STAT3, IL-23, MMP-9
Immune suppression	IL-10, STAT3, GDF-15, TnC
Blood-brain barrier	Calcium-dependent release of potassium leads to blood-brain barrier dysfunction

Neurodegeneration	Reactive astrocyte effects
Alzheimer's disease	• Reactive astrocytes internalize Aβ protein aggregates • Astrocyte-derived amyloid plaques lead to disease progression
Amyotrophic lateral sclerosis (ALS)	• Reduced expression of astrocytic glutamate transporter • Defective glutamate uptake
Huntington's disease	• Dysregulated glutamate metabolism at synapses
Parkinson's disease	• Loss of neuroprotection provided by astrocytic anti-oxidant enzymes • Exacerbates disease progression by neuronal death

Wall Poster



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