IGF-1R blocking antibody. Consistent with the shRNA study results, the colonies were reduced in size, but the number of colonies produced was unaffected. Additionally, we repeated this experiment with an analog to IGF2 that does not bind IGF-2R and obtained similar results. Altogether we conclude that the IGF-1R regulates NSP cell proliferation whereas self-renewal and maintenance are promoted by IGF2 independent of IGF-1R or IGF-2R. Supported by a Dean's Grant from NJMS awarded to SWL and F31NS065607 awarded to ANZ.

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[P2.33]

Fibroblast growth factor receptor 1 (Fgfr1) participates in postnatal interneuron development

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Keywords: Parvalbumin; Somatostatin; Apoptosis; Fgf

Fibroblast growth factors (Fgfs) and several of their receptors (Fgfr) are expressed in the developing and adult CNS. Conditional mutations for Fgfr1 were generated in radial glial cells ($Fgfr1^{f/f}$;hGfapCre+) or in earlier neuroepithelial cells ($Fgfr1^{f/f}$;NesCre+) of the CNS. Fgfr1 mutants have reduced numbers of parvalbumin and somatostatin positive interneurons by unbiased stereology, and have decreases in parvalbumin protein in adulthood. The Gad1-GFP knock-in allele was crossed into Fgfr1 mutants to trace interneuron lineages. Adult $Fgfr1^{f/f}$;hGfapCre+;Gad1-GFP mutants have fewer parvalbumin positive interneurons than $Fgfr1^{f/f}$; Gad1-GFP littermate controls. Adult Fgfr1 mutants also have fewer GFP+interneurons at adulthood, but similar numbers at P0, suggesting a postnatal loss of cells rather than a failure of interneurons to express Parvalbumin. As shown by Brdu birthdating studies at E13.5, Fgfr1 mutants showed no significant alterations in number or proliferation of interneuron progenitors. These data indicate that the prenatal development of cortical interneurons is not perturbed in Fgfr1 mutants and confirms that a loss of cortical interneurons is occurring postnatally. Fgfr1 is expressed in cortical astrocytes in the postnatal brain. We have developed an in vitro model to test whether the astrocytes of mice lacking Fgfr1 are less capable of supporting interneurons by co-culturing wild type Gad1-GFP+interneuron precursors onto astrocytes isolated from $Fgfr1^{f/f}$ control and $Fgfr1^{f/f}$;hGfapCre+neonatal mice. Astrocytes isolated from Fgfr1 mutants are impaired in supporting the development of Gad1-GFP positive neurons, in vitro. Ongoing studies are evaluating whether postnatal deletions of Fgfr1 using a tamoxifen inducible Cre driven by the hGFAP promoter can result in loss of cortical interneurons. This model may elucidate potential mechanisms of interneuron cell loss relevant to neuropsychiatric disorders that develop in infancy and adolescence.

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[P2.34]

The three hit hypothesis of schizophrenia tested in genetically selected rats exposed to early life experience and adolescent psycho-social stressor

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Keywords: Early-life adversity; Maternal care; Isolation rearing; Pre-pulse inhibition

Schzophrenia is a complex mental disorder driven by genetic and environmental risk factors. In the current study, we tested the hypothesis that the interaction between predisposing genes and early-life experience can enhance vulnerability to later-life psychosocial stressors (i.e. the three hit hypothesis of psychopathology). For this purpose we have used a pharmacogenetically selected apomorphine-susceptible rat line (APO-SUS) which displays some behavioural features of schizophrenia (Ellenbroek et al., 1995, 2002). As measure for early life experience mother-pup interaction was monitored. At adolescence (weaning), social isolation rearing served as psycho-social stressor. At adulthood, rats are tested for apomorphine-induced gnawing behaviour (dopamine sensitivity), pre-pulse inhibition (*PPI*) of the acoustic startle response (sensorimotor gating) and spontaneous alternation in a T-maze (working memory). Wistar rats served as controls.

Results: Adult APO-SUS, receiving as pups low and inconsistent maternal care, show higher gnawing scores, while PPI is comparable to controls. However, APO-SUS with the least maternal care show a PPI-deficit, and if also exposed to isolation rearing PPI is further reduced and working memory is impaired. Control animals that experienced as pups high or low maternal care display low gnawing scores. Interestingly, the Wistar offspring of high maternal care dams shows a PPI and working memory deficit if exposed to an adolescent isolation, while the combination of low maternal care and isolation displays enhanced PPI.

Our data support the three hit hypothesis: early-life adversity experience makes the genetically predisposed APOSUS animals vulnerable to later unfavourable environment. Interestingly, the findings with Wistar controls selected by maternal care history provided support for the developmental mismatch theory stating that early life experience prepares for life ahead.

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[P2.35]

Mad3 regulation of cerebellar granule cell proliferation and medulloblastoma

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Keywords: Medulloblastoma; Cerebellum; Tumor stem cell; Proliferation

Medulloblastoma is a neurodevelopmental disorder of the cerebellum and the most common pediatric brain tumor. These tumors originate from cerebellar granule neuron precursor cells (GNPs) in which the Sonic Hedgehog (Shh) pathway is over-activated by genetic mutations. During development, Shh regulates proliferation of GNPs in part via regulated expression of the proto-oncogene Nmyc. In previous work, we demonstrated that the Myc/Max/Mad family member Mad3 is a novel component of the Shh signaling