and rapidly throughout the network (Morgan and Soltesz, 2008). Although Pun et al. (2012) show that altered mTOR signaling-induced DGC abnormalities are sufficient to produce epilepsy, it remains to be determined whether they are necessary for TLE development. Nonetheless, this work establishes a strong link between relatively isolated DGC pathology and subsequent epilepsy that warrants further attention directed toward a long-sought anti-epileptogenic therapy.

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Asleep at the Switch: MEK Kinases Control Transit to Gliogenesis in Developing Cortex

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In this issue of *Neuron*, Li et al. (2012) show that the neuron/glia cell fate switch of cortical progenitors is regulated by MEK1 and MEK2. The observations resonate with recent studies on the genesis of low-grade astrocytomas and highlight neuronal support functions of astrocytes in the postnatal brain.

In what seems like a case of "unintelligent design," a wide range of growth factors and other biological response modifiers signal from the outer cell surface to the nucleus through a device that has minimal functional redundancy. In the "classic" version of the RAF/MEK/ERK signaling cascade (Figure 1), signaling from some 90 odd receptor and nonreceptor tyrosine kinases (Robinson et al., 2000) is channeled initially through a set of just three small guanosine triphosphate (GTP)-binding RAS proteins (Barbacid, 1987; McCormick, 1993). Information from RAS flows next to a set of three RAF family serine/threonine kinases and thence to the mixed function protein kinases (meaning they are capable of phosphorylating either threonine or tyrosine residues) MEK1 and MEK2. The terminal kinases in this signaling axis, ERK1 and ERK2, require phosphorylation of a critical threonine x tyrosine motif to become activated. As mixed function protein kinases, MEK1 and MEK2 are the sole practitioners of ERK activation. Activated ERKs move from cytosol into the nucleus and mark the transition from cytoplasmic to nuclear signaling (McKay and Morrison, 2007). A wide range of ERK-modulated transcription factors and "immediate early" genes regulate fundamental aspects of cell biology including proliferation, differentiation, survival, and motility.

Against this backdrop, one might imagine that targeted ablation of MEK1 and MEK2 would shut down a signaling pathway for multiple growth factors and have devastating consequences for cell growth and survival. However, in this issue of *Neuron*, Li et al. (2012) report a far more nuanced and interesting phenotype when *Mek1* and *Mek2* are ablated in cortical progenitors of developing mice. The point of departure for Li et al. (2012) is a labor-intensive set of intercrosses between a *Mek2* knockout mouse strain (notably viable and fertile) and a *Mek1* floxed mouse line. By intercrossing the *Mek1* floxed and *Mek2 null* responder mice with cell type-specific *Cre* driver mice, Li et al. (2012) were able to generate animals in which the copy number of either or both *Meks* could be represented at wild-type (WT), heterozyote, or null levels.

In initial studies, a *NestinCre* driver mouse line was used to ablate floxed

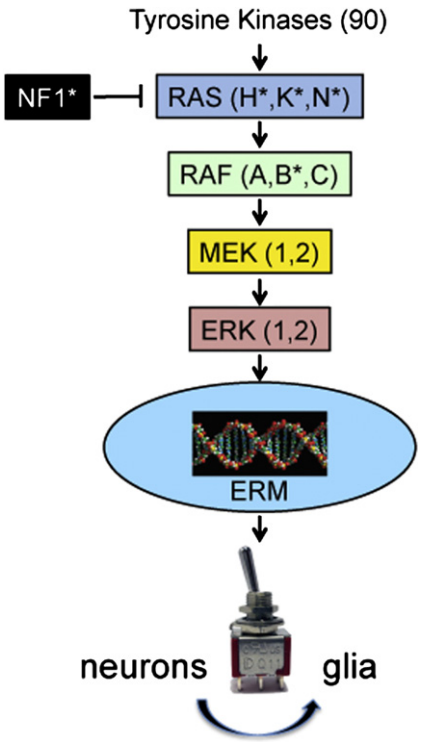

Figure 1. The "Classic" RAF/MEK/ERK Signaling Pathway and the Neuron/Glia Cell Fate Switch

The RAF/MEK/ERK signaling pathway carries signals from multiple receptors at the outer cell surface into the nucleus so as to regulate gene expression. A distinctive feature of the RAF/MEK/ERK pathway is that the number of signal carriers is constrained. Accordingly, the entire pathway can be ablated or activated by manipulation of just a few genes. Those pathway components marked by an asterisk are frequently mutated in human cancers and hereditary RASopathies so as to result in constitutive pathway activation (Barbacid, 1987; Bos, 1989; Tidyman and Rauen, 2009). Li et al. (2012) in this issue of *Neuron* show that the Ets transcription factor family member Erm is regulated by the pathway and that Erm controls the neuron/glia cell fate switch.

Mek1 in *Mek2* null radial progenitor cells. The first point noted by Li et al. (2012) is that a single copy of either *Mek1* or *Mek2* was sufficient for the genesis of viable and fertile mice (although animals sustained by only a single copy of *Mek2* are smaller than controls). The viability of the various three-allele deletion mutants suggests significant functional redundancy of the two enzymes. When both copies of *Mek1* and *Mek2* were ablated, the mice progressed through gestation and were born alive; however, they did not feed or vocalize in response to tail pinch and they died shortly after birth. Surprisingly, the *Mek1/2* null mutant brains exhibited no gross morphologic abnormalities at postnatal day (P) 0. However, astrocyte precursors marked by BLBP, Aldh1l1, and Acsbg1 were almost completely absent. Likewise missing were oligodendrocyte progenitor cells marked by Olig2 or PDGFRα.

Given the pivotal functions of MEK1 and MEK2 in growth factor signal transduction, Li et al. (2012) focused initially on excluding some of the more prosaic explanations of the phenotype. Brdu birthdating experiments showed that new neurons were being born at embryonic day (E) 17.5, long after removal of the last vestiges of floxed MEK1 protein at E11.5. Thus, the absence of glia did not reflect a general mitotic arrest. Moreover, Li et al. (2012) showed that the absence of astrocyte and oligodendrocyte progenitor cells did not reflect a simple delay in glial specification. To drive home this point, they repeated their conditional knockout experiments using *hGFAPCre* driver mice to ablate *Mek1*. The *hGFAPCre* initiates recombination at a later stage (E12.5) than *NestinCre* and the *Mek*-ablated animals consequently can survive to P10. As noted in the *NestinCre* ablation studies, the *Mek* null brains created by *hGFAPCre* appeared grossly normal at birth. However, astrocyte and olgodendrocyte precursors were again severely compromised and this deficiency was sustained all the way to P10.

The *hGFAPCre Mek* null mutants were useful in assuaging another worry. Could it be that ablation of *Mek1/2* simply reduces expression of glial markers without affecting glial specification? To address this issue, Li et al. (2012) used a recently described protocol for postnatal electroporation (Ge et al., 2012) to transduce a visual marker plasmid (pCAG-EGFP) into radial progenitors at P1. At day 7 after electroporation, enhanced green fluorescent protein (EGFP)-positive cells with clear astrocyte morphology were readily observed in the deeper cortical layers of WT mice. In contrast, mature astrocytes were not observed in the *Mek*-deleted cortices. Many of the transduced cells in *Mek*-deleted brains became neurons (rarely seen in WT brains), while a few became weakly expressing Acsbg1-positive astrocytes exhibiting abnormal morphology. These results reinforce the notion that *Mek*-deleted progenitors are defective in the classic neuron/glia fate switch and become neurons as a default fate.

In other studies, Li et al. (2012) showed that the relationship between gliogenesis and MEK function is symmetric and cell autonomous. Symmetry was demonstrated by using in utero electroporation to transduce a constitutively active mutant of *Mek1* (*caMek1*) into WT radial progenitors. The *caMek1* studies showed that MEK loss of function impairs gliogenesis, while MEK gain of function promotes gliogenesis. Cell autonomy was demonstrated by mosaic loss of function in slice cultures. Here EGFP-marked *Cre* plasmids were electroporated into E15.5 radial progenitors followed by organotypic cortical slice cultures for 4 days. The *Cre*-transduced progenitors were markedly less likely to become astrocytes than vector controls.

So how do MEKs regulate the neuron/glia switch? As indicated in Figure 1, the purpose of the RAF/MEK/ERK signaling pathway is to regulate gene expression. Microarray data sets for E18.5 cortices from WT and the *NestinCre* knockout mice were interrogated for *Mek*-responsive transcription factors. A strong candidate emerged in the form of the *Ets* transcription factor family member *Erm* (aka *ETV5*). In situ hybridization studies show intense *Erm* expression in the WT ventricular zone at E14.5–E18.5. In *Mek* null brains, expression of *Erm* is profoundly reduced in the ventricular zone. These correlative observations were followed by rescue experiments in *NestinCre*-ablated *Mek* null brains. Because these mice die at early postnatal stages, *Erm* expression vectors were electroporated ex vivo. The cortices were then dissociated and challenged with the astrogenic growth factor CNTF. The data showed that expression of *Erm* rescues CNTF-induced formation of astrocytes in *Mek* null mutant cultures. Conversely, a dominant-negative *Erm* mutation blocks formation of astrocytes in response to the constitutively active *caMek1*.

The observations of Li et al. (2012) resonate within an emerging body of data on neurofibromatosis type 1 (NF1) and sporadic low-grade astrocytomas in

children. The *NF1* gene encodes neurofibromin, a RAS GTPase that converts the GTP-bound active form of RAS proteins to the inactive, guanosine diphosphate (GDP)-bound form (Scheffzek et al., 1997). As indicated in Figure 1, loss-of-function NF1 leads to hyperactivation of the RAF/MEK/ERK pathway and is associated with neurological diseases—notably low-grade astrocytomas. Studies by Gutmann and his colleagues demonstrate that NF1 inactivation promotes astroglial differentiation (Dasgupta and Gutmann, 2005). Moreover, deleting floxed *Nf1* in neural progenitors during early embryonic stages leads to a dramatic increase in the glia cell population in the brain (Hegedus et al., 2007)—a phenotype quite similar to that of the *caMek1/hGFAP* mice described by Li et al. (2012). Another very recent study by Zhu and his colleagues reveals that deletion of *Nf1* in neural stem cells results in increased gliogenesis at the expense of neurogenesis. Importantly, the NF1-mediated glia/neuronal fate switch is due to overactivation of MEK/ERK signaling, as it can be reversed by applying small molecule inhibitors of MEK/ERK function (Wang et al., 2012). The low-grade astrocytomas seen in NF1 patients have a sporadic counterpart in children. Recent studies show that a large majority of pediatric low-grade astrocytomas have activating mutations in BRAF (see Figure 1) (Jones et al., 2008; Pfister et al., 2008).

Closer to home for the basic scientists, the observations of Li et al. (2012) present a useful new tool to the field of glial biology. Postnatal functions of astrocytes have been difficult to resolve because it has been difficult to manipulate astrocyte number during development. Li et al. (2012) note that the *NestinCre Mek* null mice are acallosal at P0 in tandem with the absence of midline astroglia. Moreover, the *hGFAPCre Mek* null animals show a neurodegenerative phenotype by day P10. For the road ahead, the *Mek* ablation and *Mek* hyperactivation models described here may provide a means of changing neuron/glia ratios to display glial functions in neuronal activity. In the fullness of time, such manipulations might even shed light on the role of glia in the cognitive aspects of NF1 syndrome and a variety of other hereditary "RASothapies" associated with mutations in core components of the signaling axis.

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Choosing for Me or Choosing for You: Value in Medial Prefrontal Cortex

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In this issue of *Neuron*, **Nicolle et al. (2012)** suggest that choice-related value signals in ventromedial and anterior dorsomedial prefrontal cortex can be distinguished by their relevance to the current choice, as opposed to their reflection of preferences ascribed to the self versus another.

Our understanding of the neural mechanisms of value-based decision making has increased dramatically in the last decade. Much of this progress has been achieved with the adoption of formal mathematical models that can be used to explain the process by which we compute values for stimuli in the world and use those values to guide our choices (Montague et al., 1996; Glimcher and Rustichini, 2004; Daw et al., 2005). By mapping components of these mathematical