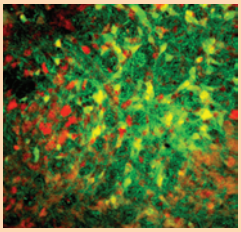
GlyRα3 keeps breathing in rhythm



Rhythmic breathing in mammals is regulated by a neuronal network in the lower brainstem. The output of this network is, in turn, controlled by coordinated integration of excitatory and inhibitory synaptic inputs. Dysfunction and/or disruption of the inhibitory inputs, such as occurs in hyperekplexia (commonly known as startle disease), following ischemia and stroke, and as a result of deep anesthesia and opiate abuse, leads to apnea. Inhibitory inputs are largely controlled by glycinergic transmission, and Manzke and colleagues have now shown that glycinergic inhibition plays a pivotal role in controlling breathing in C57BL/6 mice and identified a molecular mechanism by which the inhibitory glycine receptor α3 subtype (GlyRα3) is regulated (4118–4128). Specifically, activation of serotonin receptor type 1A (5-HTR_{1A}) was shown to induce dephosphorylation of GlyRα3, leading to enhanced glycinergic inhibition of the neuronal network controlling rhythmic breathing. Importantly, in vivo pharmacologic activation of 5-HTR_{1A} augmented inhibitory glycinergic currents transmitted via GlyRα3 and counteracted opioid-induced depression of breathing, thereby protecting against opioid-induced apnea. The authors therefore suggest that pharmacologic activation of the 5-HTR_{1A}–GlyRα3 signaling pathway might provide an approach to treating breathing disturbances caused by the wide range of disorders that disrupt inhibitory synaptic transmission.

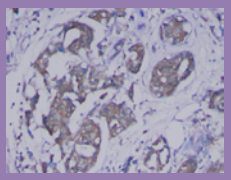
MKP-3 promotes hepatic glucose production

The excessive hepatic gluconeogenesis that occurs in insulin-resistant individuals is a key factor in their development of hyperglycemia and progression to type 2 diabetes mellitus. Recent in vitro data indicate that MAPK phosphatase–3 (MKP-3) promotes the transcription of genes encoding proteins involved in gluconeogenesis. Wu and colleagues therefore set out to investigate whether MKP-3 has similar effects in vivo (3901–3911). Initial analysis indicated that MKP-3 expression is elevated in the liver of diet-induced obese mice. Consistent with these data and the hypothesis that MKP-3 promotes gluconeogenesis, overexpression of MKP-3 in lean mice increased fasting blood glucose levels, whereas knockdown of MKP-3 expression in both lean and obese mice decreased fasting blood glucose levels. Further analysis revealed that MKP-3 induced the transcription of genes encoding proteins involved in gluconeogenesis by dephosphorylating forkhead box O1 (FOXO1), which promoted its translocation to the nucleus and subsequent induction of PPARγ coactivator–1α (*Pgc1a*) transcription. As these data indicate that MKP-3 has a key role in promoting hepatic gluconeogenesis in vivo in mice, the authors suggest that it might provide a new therapeutic target for the treatment of obesity-related hyperglycemia and type 2 diabetes mellitus.

Profiling key antiviral responders

$CD8^+$ T cells are key mediators of the antiviral immune response. The fate of these cells after a primary response varies depending on whether the virus is cleared from the body or persists and depending on the virus. In the case of persistent human CMV (HCMV) infection, a large number of virus-specific, quiescent effector-type $CD8^+$ T cells with constitutive cytolytic activity remains after a primary immune response. In this issue (4077–4090), Hertoghs and colleagues report data that suggest that the persistent effector cell properties of these cells are important in preventing HCMV reactivation. The data were generated by molecular profiling of HCMV-specific $CD8^+$ T cells collected from patients at different stages of infection. At all stages of infection, HCMV-specific $CD8^+$ T cells expressed the genes encoding the Th1-associated transcription factors T-bet and eomesodermin, the Th1 cytokine IFN-γ, and the cytolytic proteins granzyme B and perforin. Importantly, HCMV-specific $CD8^+$ T cells showed no signs of exhaustion during HCMV persistence, as is seen in chronic viral infections such as EBV and HIV. The authors therefore suggest that the phenotype of the $CD8^+$ T cells remaining after a primary viral infection depends on the protective response needed to cope with that virus.

NOS2 not good for ER-negative breast cancer patients



Breast cancers can be divided into different subtypes based on several criteria, including whether they express estrogen receptor (ER). Patients with ER-negative breast tumors have a worse prognosis than those with ER-positive breast tumors. However, even among ER-negative breast tumors, those characterized as basal-like are the most aggressive and difficult to treat. New therapeutic targets for this subtype of breast cancer are urgently needed. In this issue (3843–3854), Glynn and colleagues report data that suggest that NOS2 could be a good drug target in this context. Initial analysis indicated that increased NOS2 expression predicted poor survival in patients with ER-negative breast cancer. High NOS2 expression in ER-negative breast tumors was associated with a gene expression signature characteristic of basal-like breast cancer and predictive of poor survival. Mechanistically, NO enhanced the in vitro motility and invasion of ER-negative cells, and preliminary data suggested that NO induced activation of c-Myc, which in turn was crucial for inducing the gene expression signature characteristic of basal-like breast cancer. The authors therefore conclude that high levels of NOS2 are a predictor of survival in patients with ER-negative breast tumors and suggest that selective NOS2 inhibitors might be of benefit to these individuals.