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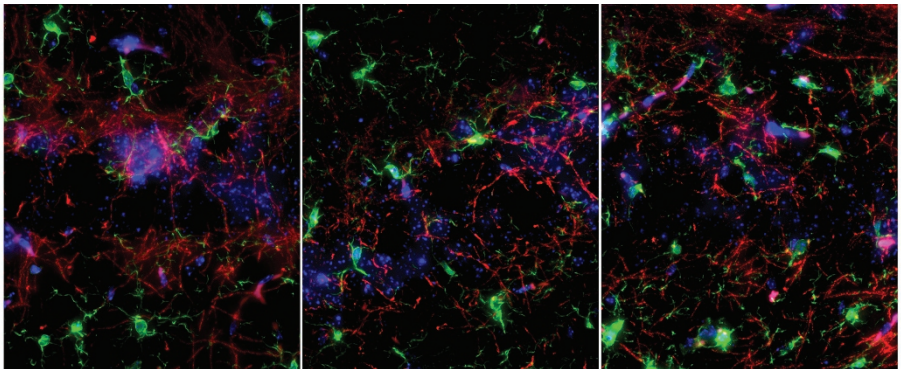


Estriol preserves hippocampus in a mouse MS model

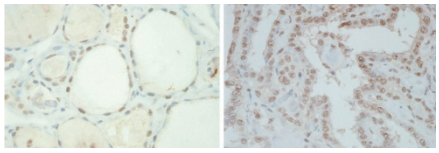
See page 1234

Many multiple sclerosis (MS) patients experience cognitive deficits and impairment of hippocampus-dependent learning and memory. *In vivo* magnetic resonance imaging and postmortem analysis have revealed hippocampal pathology in MS, but the relationship between pathology and dysfunction is not fully understood. Estriol, an estrogen that increases during pregnancy, is a therapeutic candidate because of its general positive effects on the immune and nervous systems. Interestingly, the relapse rates of MS patients decline during the third trimester of pregnancy, when estriol levels peak. Experimental autoimmune encephalomyelitis (EAE) recapitulates many of the salient features of MS, including demyelination, axonal loss, and inflammation in the central nervous system and thus serves as an excellent MS model.

Ziehn *et al* used an EAE mouse MS model to study the relationship between hippocampal proteins and excitatory synaptic transmission. They demonstrated that EAE mice had defects in basal hippocampal synaptic transmission that were linked to a decrease in the probability of presynaptic neurotransmitter release. These findings were associated with lower levels of pre- and postsynaptic proteins, providing a mechanistic explanation for decreased synaptic transmission. Furthermore, there was an increase in CA1 region axonal demyelination—a hallmark of MS—accompanied by an increase in reactive microglia. Importantly, treatment with estriol prevented biochemical, structural, and functional deficits in this EAE model, suggesting that estriol therapy might prevent or diminish the hippocampus-dependent learning and memory defects seen in MS. Further studies are needed to determine how estriol acts to prevent the pathological changes observed in the hippocampus in EAE.

RUNX2 in thyroid carcinomas

See page 1181



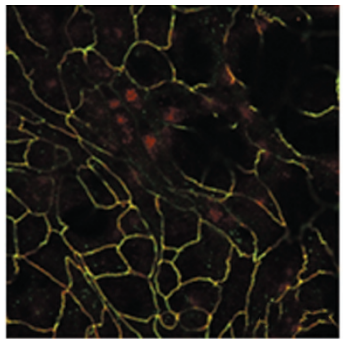
Follicular thyroid carcinomas are the most common endocrine malignancies. The family of Runt-related transcription factor (RUNX) proteins regulate proliferation and differentiation during embryonic development. The RUNX-family proteins—RUNX1, RUNX2, and RUNX3—show tissue-specific functions. Recently, a *Runx2*$^{+/-}$ heterozygous mouse was found to be hypothyroid, suggesting a role for Runx2 in thyroid development. Furthermore, RUNX2 is increasingly recognized as an oncogene in human cancers, in which it promotes metastasis through upregulation of matrix metalloproteinases, proangiogenic factors, and positive regulation of epithelial-to-mesenchymal transition (EMT).

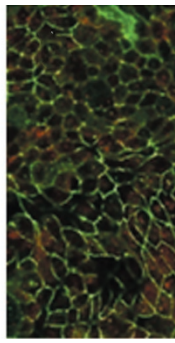
On the basis of these results, Niu *et al* sought to determine the role of RUNX proteins in thyroid carcinomas. Using tissue microarrays, they found that RUNX2 was expressed in all thyroid carcinomas, including papillary, follicular, and undifferentiated carcinoma—usually strongly—but was not usually expressed in benign thyroid neoplasms, nonneoplastic thyroid diseases, or normal thyroid. Examination of thyroid carcinoma cell lines also revealed strong *RUNX2* messenger RNA (mRNA) expression, which was dependent on mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling. Small interfering RNA (siRNA)-mediated depletion of *RUNX2* resulted in downregulation of several mRNAs involved in EMT, angiogenesis, and cell invasion. siRNA-mediated depletion of *RUNX2* resulted functionally in decreased cell invasion as measured by a Transwell invasion assay. Overall, these results suggest that RUNX2 is upregulated during thyroid carcinogenesis and that it plays important roles in metastasis through activation of EMT, angiogenesis, and cell invasion. Because RUNX2 expression is linked to MAPK/ERK signaling, ERK inhibitors may be useful in the treatment of thyroid carcinomas.

Tight-junction disruption by cytokines in airway epithelia

See page 1140

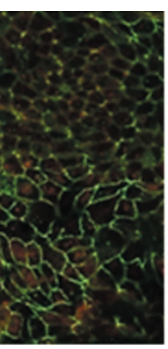
Airway epithelial cells constitute a selective barrier that restricts entry of inhaled microorganisms, irritants, and allergens. Tight junctions play a key

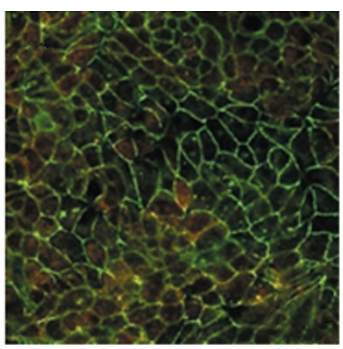




role in maintaining barrier integrity by joining the cell membranes of adjacent cells to create a physical barrier. Occludin and zonula occludens-1 (ZO-1) are two important proteins in tight junctions. There is evidence that tight-junction assembly and disassembly is regulated by intercellular signaling molecules. Specifically, proinflammatory cytokines have been found to negatively regulate tight junctions. Epidermal growth factor receptor (EGFR) signaling is known to regulate a variety of processes in airway epithelial cells. However, the relationship between tight junctions and EGFR has not been studied.

Petecchia *et al* hypothesized that proinflammatory cytokines might regulate tight junctions through EGFR signaling. They demonstrated that exposure to tumor necrosis factor-α (TNF-α), interleukin-4, or interferon-γ to Calu-3 cells resulted in downregulation of ZO-1 and occludin and an increase in paracellular conductance, indicative of decreased barrier function. Exposure to the abovementioned proinflammatory cytokines was associated with increased mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) 1/2 signaling. Because the authors suspected that EGFR and MAPK/ERK signaling might regulate tight junctions, they examined the effect of pharmacological blockade of EGFR and MAPK/ERK after exposure to proinflammatory cytokines and found that both EGFR and MAPK/ERK blockade prevented tight-junction damage. Overall, these results provide evidence that EGFR and MAPK/ERK signaling are important regulators of airway epithelial tight junctions.





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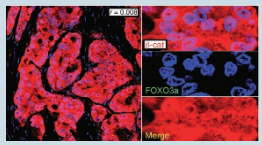
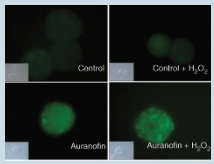
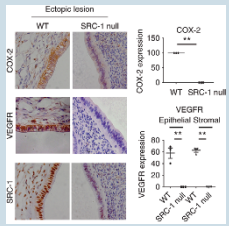


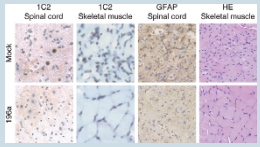
Surprising role for FOXO3a as metastasis inducer β-Catenin pathway activation by mutations is the initiating event in more than 90% of colon cancers. Forkhead box O3 (FOXO3a), a transcription factor, is considered a tumor suppressor. However, β-catenin can act as a transcriptional coactivator for FOXO3a, regulating a common set of target genes. Tenbaum *et al*, in a study recently reported in *Nature Medicine*, sought to understand the physiological relevance of the crosstalk between FOXO3a and β-catenin in colon cancer. They found that nuclear FOXO3a and β-catenin regulated a set of metastasis genes. Furthermore, colon cancer cells with nuclear FOXO3a and β-catenin exhibited increased metastasis in an orthotopic xenograft model as compared with colon cancer cells expressing β-catenin alone. These findings have profound implications for anticancer drugs that cause nuclear localization of FOXO3a, such as AKT inhibitors.
Nature Medicine 2012;18:892–901; doi:10.1038/nm.2772



Repurposing auranofin for the treatment of amebiasis *Entamoeba histolytica*, a protozoan intestinal parasite, causes human amebiasis, the fourth leading cause of death due to protozoan infections worldwide. In a recent letter in *Nature Medicine*, Debnath and colleagues explain how they overcame several technical hurdles to use high-throughput drug screening to identify new therapies for *E. histolytica*. They found that auranofin, sold as Ridaura (Prometheus), a US Food and Drug Administration (FDA)–approved oral, gold-containing drug with a long track record of clinical use for the treatment of rheumatoid arthritis, had a significant growth-inhibiting effect. Further testing in rodent models confirmed its *in vitro* efficacy. Mechanistic studies revealed that auranofin targeted *E. histolytica* thioredoxin reductase, which is involved in prevention of, intervention in, and repair of damage caused by oxidative stress. These results led to FDA designation of auranofin as an orphan drug for the treatment of amebiasis.
Nature Medicine 2012;18:956–960; doi:10.1038/nm.2758



A new isoform of SRC-1 drives endometriosis Steroid receptor coactivators (SRCs) modulate nuclear receptor–mediated cellular processes. In endometriosis, SRC-1 protein concentrations are lower than in normal endometrium. In work recently reported in *Nature Medicine*, Han *et al* investigated whether low levels of SRC-1 might be important in endometriosis. They discovered that full-length levels of SRC-1 were indeed lower in endometriosis patients—but due to replacement by a truncated 70-kDa C-terminal form of SRC-1. Further studies revealed that this SRC-1 was generated from cleavage by matrix metallopeptidase 9 (MMP9), which was activated by tumor necrosis factor-α (TNF- α). The 70-kDa SRC-1 protein facilitated endometriosis glandular cell evasion from apoptosis, epithelial–mesenchymal transition, and soft-tissue invasion, the hallmarks of endometriosis. These results highlight a potential role for the TNF-α–MMP9–SRC-1 axis in therapeutic intervention in endometriosis.
Nature Medicine, published online 3 June 2012; doi:10.1038/nm.2826



MicroRNA-based therapy for spinal and bulbar muscular atrophy Spinal and bulbar muscular atrophy (SBMA) is an inherited neurodegenerative disorder caused by expansion of the polyglutamine tract of the androgen receptor (AR). Miyazaki *et al*, in a study recently described in a letter in *Nature*, demonstrated that miR-196a was upregulated in the spinal cord in a mouse model of SBMA. They subsequently showed that miR-196b targeted AR with a 97-glutamine repeat (AR-97Q) indirectly, through targeting the messenger RNA (mRNA) of CELF2, which stabilizes AR-97Q mRNA. To test miR-196b therapeutically, the authors delivered miR-196b via an adeno-associated virus vector, which resulted in decreased disease progression. These results serve as a proof of principle for using microRNA-based therapies to treat neurodegenerative disorders caused by a single abnormal protein.
Nature Medicine, published online 3 June 2012; doi:10.1038/nm.2791