■ CANCER

Extrachromosomal resistance

A recent study looking at single cell responses of gliobastoma tumors expressing an oncogenic mutant form of endothelial growth factor receptor (EGFR) suggests that dynamic downregulation of extrachromosomal oncogenes can drive resistance to targeted therapies in cancer (*Science* doi:10.1126/science.1241328).

EGFR typically displays a heterogeneous pattern of expression, but increased amounts of mutant EGFR seem to confer sensitivity to tyrosine kinase inhibitors targeting this receptor, such as erlotinib. This may be a liability for tumor cells exposed to therapy, forcing them to eliminate mutant EGFR during treatment. Consistently with this, Paul S. Mischel and his colleagues found decreased amounts of EGFR in the cells of tumor-bearing animals and patients treated with erlotinib. The downshift in EGFR levels during erlotinib treatment came from the loss of extrachromosomal mutant EGFR, which is typically a source of the oncogenic receptor, and did not diminish the tumor formation capability of glioma cells. After treatment cessation, the mutated EGFR extrachromosomal elements increased again, rendering cells sensitive to erlotinib and highlighting the ability of tumor cells to fine-tune oncogene levels to adapt to adverse conditions.

The results underscore the importance of tumor heterogeneity in maintaining a dynamic, flexible ratio of oncogene expression that maximizes tumor fitness, both by population selection and by autonomous cellular regulation. Extrachromosomal elements may thus provide an additional layer of adaptation to therapy that should be accounted for in designing anticancer treatments. —*VA*

■ AUTISM

Bacterial link to autistic behaviors

Children with autism commonly have gastrointestinal comorbidities; Elaine Y. Hsiao and her colleagues now show that treating a maternal immune–mediated mouse model of autism with probiotics can restore both gut barrier function and behavioral abnormalities in the mice (*Cell* **155**, 1451–1463, 2013).

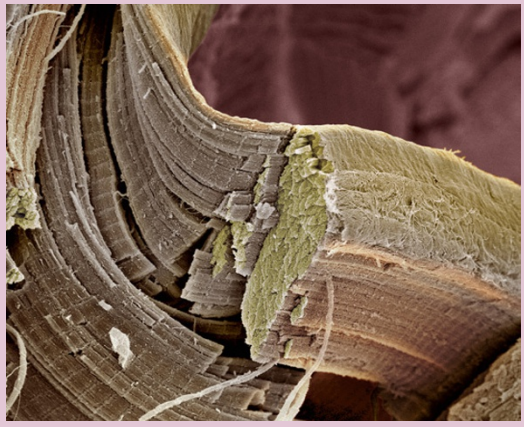
The researchers activated the immune system of pregnant mice by injecting them with a viral-like molecule. The offspring exhibited many behavioral features of autism, such as enhanced anxiety and decreased ultrasonic vocalizations, as well as gut barrier dysfunction and a shift in some bacterial species in the gut. When the young offspring were treated with the human gut commensal organism *Bacteroides fragilis* as a probiotic, the bacterial balance was restored, as was gut barrier function and autism-like behavioral symptoms.

One particular serum metabolite produced by some mouse gut bacteria, 4-ethylphenylsulfate, was markedly increased in the autism model offspring, and the amounts were after treatment with the probiotic. Injection of this metabolite into normal mice resulted in a subset of behavioral abnormalities that had been seen in the autism model offspring, such as anxiety, suggesting that this metabolite, perhaps in combination with others, affects some neural circuits linked to autism. The direct relevance of this study to other mouse models of autism remains to be determined. —*EC*

SKELETAL MUSCLE

Muscular T_{reg} cells

Inflammatory processes regulate muscle regeneration in response to injury and disease. A new study shows that a subset of regulatory T (T_{reg}) cells accumulates in the muscle shortly after injury and helps promote tissue repair (*Cell* 155, 1282–1295, 2013).



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Using mouse models of both acute injured skeletal muscle and muscular dystrophy, Dalia Burzyn and her colleagues found that a population of T_{reg} cells with specific functional and gene expression profiles accumulates at the site of injury just as newly recruited myeloid cells in the muscle convert from a pro- to an anti-inflammatory state and the muscle is beginning to regenerate. Muscle regeneration is impaired in injured mice lacking these T_{reg} cells, and depletion of T_{reg} cells in the muscle inhibited the phenotypic switch in myeloid cells, increased proinflammatory lymphocyte recruitment to the muscle and impaired the myogenic activity of muscle progenitor cells. These muscle T_{reg} cells expressed the growth factor amphiregulin, which activated differentiation of muscle satellite cells into muscle fibers in myogenic assays.

Although it remains unclear how this subset of T_{reg} cells is recruited to the muscle and whether other mechanisms or factors promote muscle regeneration, the findings uncover both immunological and nonimmunological roles for T_{reg} cells during muscle repair. —*CP*

■ VACCINES

Vaccine stresses out DCs

The yellow fever vaccine, YF-17D, promotes antiviral T cell responses by activating the stress response and autophagy in dendritic cells (DCs), according to a recent study in *Science* (doi:10.1126/science.1246829).

General control nonrepressed 2 kinase (GCN2) senses amino acid starvation and regulates the stress response. Early induction of GCN2 in response to yellow fever vaccination is associated with the $CD8^+$ T cell response, suggesting GCN2 may orchestrate the adaptive immune response to vaccination.

Bali Pulendran and his colleagues now show that YF-17D induces GCN2 expression in human DCs, which then activates the stress response. Mice lacking GCN2 specifically in DCs developed an attenuated $CD8^+$ and $CD4^+$ T cell response after vaccination. Culture of DCs with YF-17D also induced autophagy and promoted antigen presentation in these cells in a GCN2-dependent manner. Inhibition of autophagy impaired cross-presentation and priming of $CD4^+$ and $CD8^+$ T cells. These findings suggest that one mechanism underlying the protective effects of the YF-17D vaccine may be the induction of the stress response, autophagy and antigen presentation by GCN2 in DCs. —*KDS*

Written by Victoria Aranda, Eva Chmielnicki, Kevin Da Silva & Carolina Pola