■ DEVELOPMENTAL DISORDERS

p53 and CHARGE syndrome

CHARGE syndrome is a developmental disorder presenting with many phenotypes such as heart defects and ear abnormalities. A recent study has found a role for p53 in the development of these phenotypes and provides a new mouse model to study the disease (*Nature* doi:10.1038/nature13585).

Jeanine L. Van Nostrand and her colleagues observed that mice expressing both wild-type p53 and a mutant form that is transcriptionally inactive but stabilized are embryonically lethal. These mice presented a wide range of developmental defects characteristic to CHARGE syndrome. Furthermore, in mouse embryonic fibroblasts derived from these mouse embryos, the mutant protein was itself found to stabilize the wild-type protein, resulting in its hyperactivation. This drove elevated expression of certain p53 targets, which most likely drives the increased apoptosis and reduced proliferation seen in affected tissues.

The transcriptional regulator CHD7 is known to be mutated in 70–90% of CHARGE syndrome cases. The authors found that CHD7 negatively regulated p53 expression in mice neural crest cells and that p53 was hyperactivated in these cells and in patient samples. Furthermore, the phenotypes of mice lacking Chd7 could be partially alleviated by p53 heterozygosity. Thus, the authors conclude that inappropriate activation of p53 has a crucial role in the development of CHARGE syndrome phenotypes. —*HS*

■ DEPRESSION

miR135 promotes resilience

A new study suggests that microRNA 135 (miR135) is protective against stress-induced depression-like behaviors and mediates the effects of some antidepressant drugs (*Neuron* **83**, 344–360).

Dysregulation of serotonin (5HT) signaling is strongly implicated in mood disorders. By comparing the miR profiles of 5HT and non-5HT mouse midbrain raphe nuclei (RN) neurons, Orna Issler and her colleagues identified miR135 as a repressor of two genes associated with 5HT signaling. Treatment with 5HT-targeting antidepressants increased expression of miR135a, the predominant allele in the mouse brain. Overexpression of miR135a in 5HT neurons protected against increased anxiety and depression-like behaviors in mice following chronic social defeat stress. miR135a overexpression also decreased 5HT levels and increased 5HT metabolism in the mouse brain, consistent with increased firing of 5HT neurons. Conversely, reducing miR135a levels in the RN exacerbated anxiety-like behavior and blunted the response to antidepressant treatment.

The authors found that circulating miR135a is decreased in depressed patients and increased in depressed patients that underwent cognitive behavioral therapy. Postmortem analysis also identified downregulation of mi135a in the brains of depressed suicide victims. This suggests that mi135a regulates normal 5HT tone and may be a promising drug target or biomarker for depression. —*FC*

■ INFLAMMATION

IFN's anti-inflammatory effects

An oxysterol produced in response to type I interferon (IFN) signaling suppresses inflammasome activation, according to a report in *Science* (**345**, 679–684).

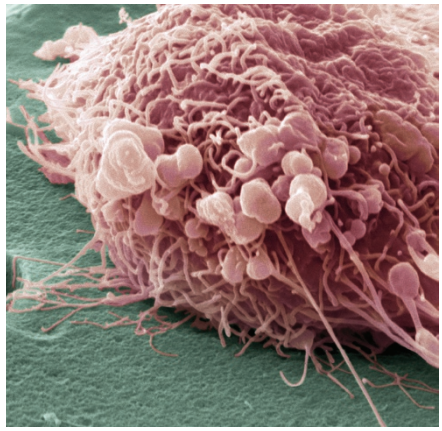
Although IFN signaling induces antiviral activity, a negative feedback pathway is also induced downstream of IFN to quell the inflammatory response and reduce interleukin-1β (IL-1β) production. Many IFN-stimulated genes are induced during an inflammatory response, but the direct contribution of particular genes to the anti-inflammatory effects of IFN remains unclear.

Jason G. Cyster and his colleagues report that one of these IFN-stimulated genes, which encodes the enzyme cholesterol 25-hydroxylase (*Ch25h*), is induced in macrophages upon stimulation with lipopolysaccharide (LPS). Upon induction, Ch25h hydroxylates cholesterol, resulting in the production of the oxysterol, 25-hydroxycholsterol (25-HC). Mice deficient in Ch25h produce more IL-1β after *in vivo* treatment with LPS and die earlier than wild-type mice. These mice also developed more severe neuroinflammatory disease and had increased frequencies of IL-17A$^+$ T cells. As a result of increased IL-1β production and inflammasome activity, *Ch25h*$^{-/-}$ mice are resistant to infection with *Listeria monocytogenes*. Mechanistically, 25-HC reduces *il1b* transcription and inflammasome activity. As IFN is commonly used to treat autoimmune disease, these findings provide some clues into the anti-inflammatory effects of IFN. —*KDS*

■ CANCER

An estrogen receptor for survival

In a recent study, Bin Yuan and his colleagues show that the presence of estrogen receptor β (ERβ) phosphorylated at Tyr36 could predict disease-free survival and overall survival in breast cancer and mediates the anti-tumor effects of ERβ (*J. Clin. Invest.* **124**, 3378–3390).



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The authors identified EYA2 and c-ABL as the respective phosphatase and kinase that regulate ERβ Y36 phosphorylation and, thus, control its downstream transcriptional activity. Wild-type ERβ significantly reduced the growth of human breast cancer cells and MDA-MB-231 breast cancer xenografts. A phosphomimetic mutant of ERβ could function similarly; however, a mutant that could not be phosphorylated was unable to control growth. Both EYA2 overexpression and c-ABL knockdown enhanced xenograft growth in the presence of wild-type ERβ, but they were unable to affect phosphomemetic mutant-mediated growth suppression.

In human breast cancer, increased phsopho-Y36 staining positively correlated with longer disease-free status and overall survival as well as negatively correlated with tumor size, nodal status, advanced disease stage and increased tumor grade. Staining was more prognostic in stage 2 and 3 breast cancer than in stage 1.

Both EYA2 and c-ABL have additional functions in tumors, but this study suggests that they could be targeted to enhance ERβ-mediated growth suppression and lead to new treatment regimens in the future. —*KS*

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