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In This Issue

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In this issue

Symptoms of Noonan syndrome ameliorated in mice Noonan syndrome (NS) is a relatively common autosomal dominant genetic disorder that is characterized by short stature, unique facial features, and congenital heart disease. Approximately 10%–15% of affected individuals have mutations in son of sevenless 1 (SOS1), which encodes a guanine nucleotide exchange factor for RAS and RAC. As with all other known NS-associated genetic mutations, SOS1 mutations lead to increased RAS/MAPK pathway signaling. In this issue (4353–4365), Chen and colleagues report the generation of a mouse model of NS caused by SOS1 mutations — knockin mice expressing the NS-associated Sos1E846K gain-of-function mutation. Homozygosity for the mutation led to multiple cardiac defects, similar to those in humans with NS, and substantial embryonic lethality. As in individuals with NS, heterozygosity for the mutation caused cardiac defects, short stature, and facial dysmorphia. In addition to Ras/MAPK pathway activation in hearts from mutant mice, Rac and Stat3 were activated. Importantly, prenatal treatment with a small-molecule MAPK kinase inhibitor reduced the embryonic lethality of homozygosity for this mutation and ameliorated the cardiac defects. The authors therefore suggest that targeting this pathway might be of benefit to individuals with NS. Easy access for cholera toxin via flotillin proteins The profuse watery diarrhea that typifies cholera is caused by cholera toxin (CT), a protein secreted by the pathogenic […]

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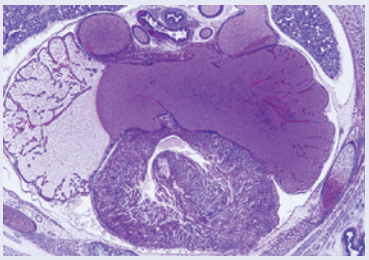
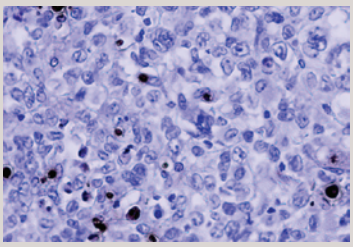


Noonan syndrome (NS) is a relatively common autosomal dominant genetic disorder that is characterized by short stature, unique facial features, and congenital heart disease. Approximately 10%–15% of affected individuals have mutations in son of sevenless 1 (*SOS1*), which encodes a guanine nucleotide exchange factor for RAS and RAC. As with all other known NS-associated genetic mutations, *SOS1* mutations lead to increased RAS/MAPK pathway signaling. In this issue (4353–4365), Chen and colleagues report the generation of a mouse model of NS caused by *SOS1* mutations — knockin mice expressing the NS-associated Sos1E846K gain-of-function mutation. Homozygosity for the mutation led to multiple cardiac defects, similar to those in humans with NS, and substantial embryonic lethality. As in individuals with NS, heterozygosity for the mutation caused cardiac defects, short stature, and facial dysmorphia. In addition to Ras/MAPK pathway activation in hearts from mutant mice, Rac and Stat3 were activated. Importantly, prenatal treatment with a small-molecule MAPK kinase inhibitor reduced the embryonic lethality of homozygosity for this mutation and ameliorated the cardiac defects. The authors therefore suggest that targeting this pathway might be of benefit to individuals with NS.

Rational design of antilymphoma therapy

Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma. New drug targets are needed for this aggressive disease because current therapies fail to cure 40% of patients. One promising target is B cell lymphoma 6 (BCL6), as the gene encoding it is a critical DLBCL oncogene. Indeed, a retro-inverted BCL6 peptide inhibitor (RI-BPI) has been shown to potently kill DLBCL cells. Cerchietti and colleagues have now improved upon these antilymphoma effects by combining RI-BPI with either a histone deacetylase inhibitor or an Hsp90 inhibitor (4569–4582). Both combinations enhanced killing of primary human DLBCL cells in vitro relative to the use of RI-BPI alone and potently suppressed the growth of established human DLBCL xenografts in mice. The authors determined that BCL6 directly repressed histone acetyltransferase p300 and its cofactor, HLA-B–associated transcript 3. RI-BPI induced expression of p300 and acetylation of key p300 targets, including p53 and Hsp90, which explains why these drug combinations were so effective. These data provide a rational basis for a potential new combinatorial therapy for DLBCL.



Promoting regression of atherosclerotic plaques

Atherosclerosis is a leading cause of death in the developed world. Treatment with statins, which lower LDL levels, delays or halts disease progression, but has little effect on existing plaques and risk of morbidity and mortality. By studying plaque regression in the *Apoe*$^{-/-}$ mouse model of atherosclerosis, Feig and colleagues hope to identify potential new targets for therapies that could reduce plaque burden (4415–4424). Previous analysis in mice indicates that plaque regression in a transplant model and an *Apoe*$^{-/-}$ mouse model involves CCR7-dependent emigration of CD68$^+$ monocyte-derived cells from plaques and that this is associated with increased levels of LXRα-encoding mRNA in plaque CD68$^+$ cells. Now, Feig and colleagues have provided several lines of evidence demonstrating that LXR signaling induces *Ccr7* expression in plaque bone marrow–derived CD68$^+$ cells and that this is atheroprotective because it promotes CD68$^+$ cell emigration from plaques. The observation that both isoforms of LXR (LXRα and LXRβ) were needed for maximal egress of CD68$^+$ cells from plaques has important therapeutic implications, as LXRα stimulation increases hepatic lipogenesis. Thus, the authors suggest that it might be necessary to develop ways to specifically target LXR agonists to CD68$^+$ cells in order to promote atherosclerotic plaque regression.

Easy access for cholera toxin via flotillin proteins

The profuse watery diarrhea that typifies cholera is caused by cholera toxin (CT), a protein secreted by the pathogenic bacterium *Vibrio cholerae*. To mediate this life-threatening effect, CT must enter the cytosol of intestinal epithelial cells. It does this by co-opting a lipid-based sorting pathway that carries it from the plasma membrane, via the *trans*-Golgi network (TGN), into the ER. At this point, a portion of CT unfolds and accesses the cytosol by retro-translocation across the ER membrane. Exactly how these trafficking steps are regulated at the molecular level has remained unclear. In this issue (4399–4409), Saslowsky and colleagues have determined that flotillin-1 and -2 — proteins thought to be involved in lipid trafficking — are required for CT-induced toxicity in zebrafish. However, Derlin-1 — a protein thought to be used by CT to usurp retro-translocation machinery — was dispensable. Furthermore, in mammalian cells, the flotillins were found to be necessary for the transport of CT from the plasma membrane to the ER via a pathway that did not involve the TGN. These surprising data lead the authors to suggest a revised model for how CT enters host cells.