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In This Issue

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Humanized mice help break down drug metabolism The expression of several enzymes that metabolize xenobiotics — entirely synthetic chemicals and drugs — is regulated by the closely related orphan nuclear hormone receptors pregnane X receptor (PXR) and constitutive androstane receptor (CAR). To model the relative importance of PXR and CAR in drug metabolism in humans, Scheer and colleagues generated mice lacking either PXR or CAR as well as mice expressing either human PXR or CAR under the control of the mouse Pxr and Car promoters, respectively (pages 3228–3239). Importantly, engineering the Pxr and Car loci to express PXR and CAR, respectively, rendered the mouse genes nonfunctional. The four mouse strains generated were then used to create mice of all possible genetic combinations, including mice expressing both human PXR and human CAR and mice lacking both PXR and CAR. The panel of mice was then used to demonstrate that upregulation of drug-metabolizing enzymes by the barbiturate phenobarbital is mediated by only CAR, contrary to results of previous in vitro studies that indicated a role for both PXR and CAR. The authors hope this panel of mice will help model how drugs are metabolized in humans, providing important information regarding probable toxicity and efficacy. Role of hepatic versus all cannabinoid receptors Endocannabinoids have been implicated in the development of many effects of […]

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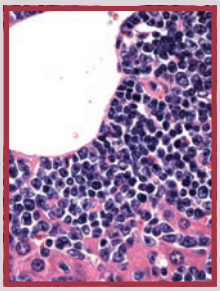
Some T cell leukemias are addicted to Notch



Although gain-of-function *NOTCH1* mutations are found in a large proportion of individuals with T cell acute lymphoblastic leukemia/lymphoma (T-ALL), it is not known whether these mutations generate downstream signals of sufficient strength to initiate disease. To address this issue, Chiang and colleagues generated mice with hematopoietic cells expressing different T-ALL–associated gain-of-function *NOTCH1* alleles (pages 3181–3194). Leukemia developed efficiently in mice with hematopoietic cells expressing *NOTCH1* gain-of-function alleles that encode a Notch1 protein able to initiate strong downstream signals; these mutations are relatively uncommon in individuals with T-ALL. Conversely, the more common mutant alleles, which encode Notch1 proteins that initiate far weaker downstream signals, did not induce leukemia. However, these mutations accelerated the onset of leukemia induced by expression of constitutively active K-ras. Thus, although the downstream signals generated by the proteins encoded by the gain-of-function *NOTCH1* alleles found most commonly in individuals with T-ALL are not of sufficient strength to initiate leukemia development, they are of sufficient strength to complement other leukemogenic events, such as activation of K-ras; moreover, inhibition of the Notch signaling pathway in this context abrogated tumor growth. The authors therefore suggest that their findings support the evaluation of Notch signaling pathway inhibitors as potential treatments for leukemia.

Role of hepatic versus all cannabinoid receptors

Endocannabinoids have been implicated in the development of many effects of a high-fat diet, including obesity, fatty liver (hepatic steatosis), insulin resistance, leptin resistance, and dyslipidemia. However, whether the effects of endocannabinoids are mediated by activation of the cannabinoid receptor CB_1 in the CNS, liver, or other peripheral tissues has not been determined. To address this issue, Osei-Hyiaman and colleagues generated mice lacking CB_1 in hepatocytes (pages 3160–3169). Similar to wild-type mice, when these mice were fed a high-fat diet they became obese. However, they exhibited less severe hepatic steatosis, insulin resistance, leptin resistance, dyslipidemia, and hyperglycemia than did the wild-type mice. These data indicate that although activation of CB_1 in the liver does not contribute to the development of high-fat diet–induced obesity, it does contribute to the development of high-fat diet–induced hepatic steatosis, which increases the risk of developing cirrhosis of the liver, and to the hormonal and metabolic changes that occur as a result of such a diet, increasing the risk of type 2 diabetes. The authors therefore suggest that targeting peripheral CB_1 might provide an effective way to treat obesity-related medical conditions without the side effects of targeting CB_1 in the CNS: anxiety and depression.

Beating of the heart: differentially regulated in atria and ventricles

Contraction of the heart is controlled by several pathways, including one initiated by stimulation of β-adrenergic receptors. At the molecular level, the flow of Ca^{2+} through L-type Ca^{2+} channels has a role in the initiation of contraction of the heart as well as in the regulation of contraction by β-adrenergic pathways. While previous data indicate that stimulation of β_3-adrenergic receptor (β_3-AR) decreases the contractility of human ventricle tissue and the activity of ventricle L-type Ca^{2+} channels in animal models, Skeberdis and colleagues now show that β_3-AR stimulation increases the activity of L-type Ca^{2+} channels in isolated human atrial myocytes (HAMs) and the contractility of human atrial tissue (pages 3219–3227). These conclusions were reached following in vitro analysis of the effects of two β_3-AR–specific agonists, a β_3-AR partial agonist, and a β_3-AR antagonist (as well as a β_1-/β_2-AR antagonist and a β_1-/β_2/β_3-AR antagonist) on the flow of Ca^{2+} through L-type Ca^{2+} channels in single HAMs and the contractility of human atrial tissue. Further experiments determined that these effects of β_3-AR stimulation are mediated via a cAMP-dependent pathway. The demonstration that β_3-AR stimulation has opposing effects on human atrial and ventricular tissue has important implications for those developing therapeutics targeting β-adrenergic receptors for the treatment of cardiovascular diseases.