JCI The Journal of Clinical Investigation

Amendment history:
- Erratum (November 2010)

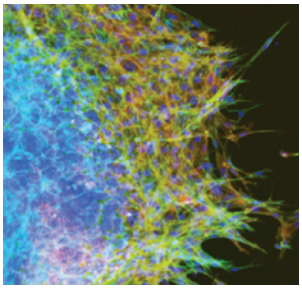
In This Issue

J Clin Invest. 2010;120(10):3403-3403. https://doi.org/10.1172/JCI44978.

In this issue

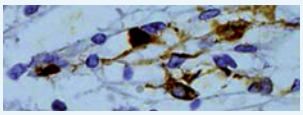
Pathway to polycystic kidney disease Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder characterized by the formation of multiple cysts in the kidneys that can cause chronic renal failure. It is caused by mutations in one of two loci, polycystin 1 (PKD1) and polycystin 2 (PKD2). The precise molecular mechanisms underlying cystogenesis have not been determined, although some data suggest a role for hyperactivation of mammalian target of rapamycin (mTOR). In this issue (3617–3628), Qin and colleagues delineate the pathway responsible for mTOR hyperactivation in a mouse model of ADPKD and demonstrate that this pathway leads to cystogenesis. Initial analysis indicated that mTOR hyperactivation in Pkd1-null mouse cells occurred downstream of the hepatocyte growth factor (HGF) receptor c-Met. Further analysis revealed that Pkd1-null mouse cells expressed increased levels of c-Met because it was not properly ubiquitinated and degraded. This in turn was because the E3-ubiquitin ligase Casitas B-lineage lymphoma (c-Cbl) was sequestered in the Golgi apparatus. As use of a pharmacologic inhibitor of c-Met inhibited mTOR activity and blocked cystogenesis in a mouse model of ADPKD, the authors suggest that blockade of c-Met could provide a new […]

A Notch(1) in the road to understanding heart valve formation



The most commonly diagnosed congenital heart defects are cardiac valve malformations. Understanding the molecular mechanisms underlying valve development should provide new avenues of research into the origin of cardiac valve defects. In this context, Luna-Zurita and colleagues have determined that integration of endocardial-Notch1 and myocardial-Bmp2 signals in prevalvular regions of the mouse heart is critical to embryonic cardiac valve formation (3493–3507). In higher vertebrates, heart valve primordia are generated from endocardial cells that undergo epithelial-to-mesenchyme transition (EMT). In the study, Luna-Zurita and colleagues show that during cardiac valve formation, EMT is limited to prospective valve territories by the interplay between endocardial-Notch1 and myocardial-Bmp2 to regulate the Snail1 transcription factor. Constitutive Notch1 activity in endocardial cells initiated a partial (noninvasive) Snail1-driven EMT in vitro that became invasive upon Bmp2 treatment. In addition, ectopic myocardial Notch1 expression and loss-of-function experiments indicated that Notch1 represses *Bmp2* in cardiac cells while *Bmp2* inactivation in the myocardium impaired Notch1 activity. This embryonic Notch1/Bmp2/Snail1 relationship may also be relevant in adult valve disease or atherosclerosis, as these diseases share features such as tissue inflammation, EMT, fibrosis, and calcification.

Lack of cell movement links four developmental disorders

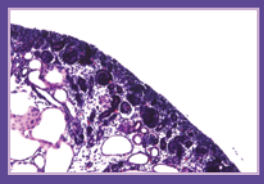


Kallmann syndrome is a developmental disorder characterized by hypogonadotropic hypogonadism and a defective sense of smell as a result of an absence of olfactory bulbs, a condition known as arrhinencephaly. It has been suggested that hypogonadism is caused by failed embryonic migration of neurons producing gonadotropin-releasing hormone 1 (GnRH1) from the nasal epithelium to the forebrain. In this issue (3668–3672), Teixeira and colleagues show that failed embryonic migration of GnRH1-producing neurons is a common feature of several developmental disorders that include arrhinencephaly, specifically X-linked Kallmann syndrome, CHARGE syndrome, trisomy 13, and trisomy 18. Immunohistochemistry analysis of fetuses with these disorders indicated that there were few or no GnRH1-producing neurons in the preoptic and hypothalamic regions of arrhinencephalic fetuses, whereas large numbers of these cells were present in control fetuses. Instead, these cells accumulated in the frontonasal region of the brain, which is the first step of the GnRH neuronal migratory path. As interrupted olfactory nerve fibers were also detected in this region, the authors conclude that the failed migration of GnRH1-producing neurons observed in all four arrhinencephalic disorders studied occurs as a result of a primary embryonic failure of peripheral olfactory structures.

Knock down Cbl-b: knock down obstacles to leukemia therapy

One approach being developed as a treatment for malignant disease is adoptive transfer of ex vivo–expanded autologous tumor-specific $CD8^+$ T cells. Although this approach has been effective in some patients, several issues, including poor in vivo survival and function of the transferred cells, have limited further clinical use. A potential way to improve the efficacy of adoptive immunotherapy is described in this issue by Stromnes and colleagues (3722–3734). In a mouse model of disseminated leukemia, it was found that abrogating expression of Casitas B-lineage lymphoma b (Cbl-b), a negative regulator of lymphocyte activation, in tumor-specific $CD8^+$ T cells expanded ex vivo increased their therapeutic effects upon adoptive transfer. The enhanced therapeutic effects of tumor-specific $CD8^+$ T cells lacking Cbl-b were a result of their restored ability to produce IL-2, decreased threshold for activation, improved survival, and enhanced proliferative responses. As knocking down Cbl-b expression in human $CD8^+CD28^-$ effector T cell clones had similar in vitro effects, the authors suggest that reducing Cbl-b expression in tumor-specific $CD8^+$ T cells destined for adoptive therapy might improve their therapeutic efficacy.

Pathway to polycystic kidney disease



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