

## In This Issue

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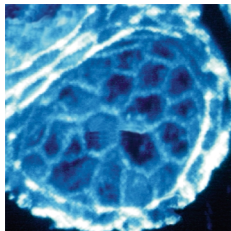
### In this issue

In the thick of the thyroid. Proper function of the thyroid depends on cycles of synthesis of the prohormone thyroglobulin followed by its proteolytic degradation. Proteolysis of thyroglobulin occurs after exposure to cysteine proteinases such as the cathepsins. In order to determine which of the cysteine proteinases are important, Klaudia Brix and colleagues have analyzed cathepsin-deficient mice (pages 1733–1745). Thyroid epithelial cell morphology, cathepsin expression and distribution, the molecular status of thyroglobulin, and serum levels of thyroxine were analyzed in mice with single or double deficiencies in the various proteases. The results suggest that cathepsins B and L are most important for solubilization of thyroglobulin from its covalently cross-linked storage form, whereas cathepsins K and L are essential for thyroxine liberation. Targeting treatment of prostate cancer. Prostate cancer is difficult to treat, due to the progression from androgen-dependent to androgen-independent tumors. Androgen suppression is the most successful treatment; however, as androgen-independent cells are insensitive to this treatment, they continue to grow. Natalia Prevarskaya and colleagues (pages 1691–1701) have identified a new target for intervention in finding that human prostate cancer cells express  $\alpha 1$ -adrenergic receptors ( $\alpha 1$ -ARs). The role for  $\alpha 1$ -ARs was previously limited to controlling contraction of prostate smooth muscle cells, but the authors now show that  $\alpha 1$ -ARs are functionally coupled to the members of store-independent diacylglycerol gated transient receptor potential (TRP) [...]

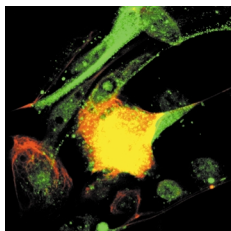
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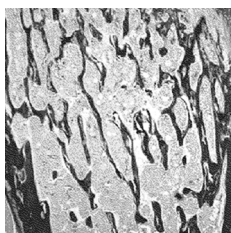




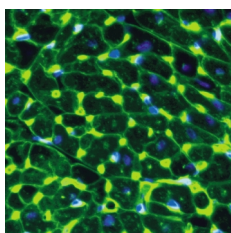
**In the thick of the thyroid.** Proper function of the thyroid depends on cycles of synthesis of the prohormone thyroglobulin followed by its proteolytic degradation. Proteolysis of thyroglobulin occurs after exposure to cysteine proteinases such as the cathepsins. In order to determine which of the cysteine proteinases are important, Klaudia Brix and colleagues have analyzed cathepsin-deficient mice (pages 1733–1745). Thyroid epithelial cell morphology, cathepsin expression and distribution, the molecular status of thyroglobulin, and serum levels of thyroxine were analyzed in mice with single or double deficiencies in the various proteases. The results suggest that cathepsins B and L are most important for solubilization of thyroglobulin from its covalently cross-linked storage form, whereas cathepsins K and L are essential for thyroxine liberation.



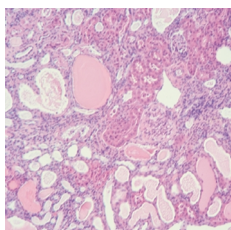
**Targeting treatment of prostate cancer.** Prostate cancer is difficult to treat, due to the progression from androgen-dependent to androgen-independent tumors. Androgen suppression is the most successful treatment; however, as androgen-independent cells are insensitive to this treatment, they continue to grow. Natalia Prevarskaya and colleagues (pages 1691–1701) have identified a new target for intervention in finding that human prostate cancer cells express  $\alpha 1$ -adrenergic receptors ( $\alpha 1$ -ARs). The role for  $\alpha 1$ -ARs was previously limited to controlling contraction of prostate smooth muscle cells, but the authors now show that  $\alpha 1$ -ARs are functionally coupled to the members of store-independent diacylglycerol gated transient receptor potential (TRP) channel family.  $\alpha 1$ -AR antagonists and TRP channel inhibitors can be developed as potential antitumor agents in the treatment of prostate cancer.



**Building bones.** Bone formation is a complex process, regulated by growth factors that are expressed by bone cells, incorporated into the bone matrix, and released in active form when bone resorbs. Ross Garrett and colleagues (pages 1771–1782) have now discovered how to accelerate bone formation by manipulating specific steps in this process. The authors inhibited the chymotryptic component of the ubiquitin-proteasomal pathway, which is the main mechanism for degradation of many proteins. Levels of bone morphogenetic protein-2 protein and gene expression were enhanced by inhibitor treatment. These results point to a potential molecular target for future drug discovery for agents that enhance the formation of bone in treatment of diseases like osteoporosis.



**How to make the heart grow.** Catecholamines such as norepinephrine, signaling through adrenergic receptors (ARs)  $\alpha 1$ ,  $\alpha 2$  and  $\beta$ , have been shown to play a role in pathological hypertrophy, but their role in physiological hypertrophy during development is less well studied. To test the hypothesis that  $\alpha 1$ -ARs are required for hypertrophy, Paul Simpson and colleagues (pages 1783–1791) generated a double knockout of the two main  $\alpha 1$ -AR subtypes in the heart, the  $\alpha 1A/C$  and the  $\alpha 1B$ . The authors found a load-independent and sex-specific requirement for  $\alpha 1$ -ARs in developmental hypertrophy and in the cardiac response to stress and implicate extracellular signal-regulated kinase (Erk) signaling in this effect. The authors conclude that  $\alpha 1$ -ARs are required for the physiological hypertrophy of normal postnatal cardiac development.



**Knocking out actinin in the kidney.** Focal and segmental glomerulosclerosis (FSGS) describes a common pattern of renal injury. One form of the disease is caused by mutations in *ACTN4*, encoding  $\alpha$ -actinin-4. This form of FSGS is highly penetrant, leading to proteinuria and renal insufficiency in adulthood. Martin Pollak and colleagues have now developed a mouse lacking detectable *Actn4* expression (pages 1683–1690), which develops progressive glomerular disease. The cellular abnormalities are not limited to the kidney, as leukocytes from these mice demonstrate increased chemokinesis and chemotaxis. The findings demonstrate that  $\alpha$ -actinin-4 has a nonredundant role in cell movement and is required for normal podocyte function. This mouse provides a model both for the further study of  $\alpha$ -actinin-4 and for studies of FSGS.