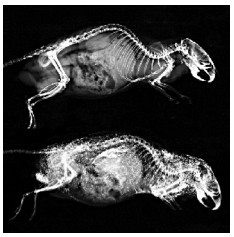
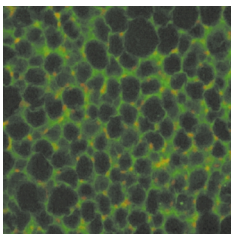
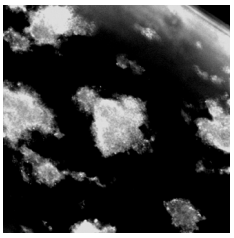


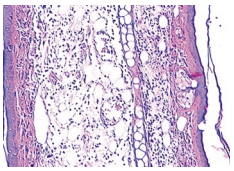
Just a fetuin-A keeps the calcium away. Ectopic calcification is a frequent complication of degenerative diseases. Willi Jahnen-Dechent and colleagues now identify the serum protein α2–Heremans-Schmid glycoprotein (Ahsg)/fetuin-A as the first systemically acting inhibitor of ectopic calcification (pages 357–366). The authors investigate Ahsg-deficient mice, which are phenotypically normal, but which develop severe calcification of various organs on a mineral-rich diet and on a normal diet when the Ahsg-deficiency is combined with a DBA/2 genetic background. This phenotype is not caused by changes in calcium and phosphate homeostasis, but by the decreased inhibitory activity of the remaining serum proteins on mineral formation. These findings demonstrate a critical role of Ahsg as an inhibitor of unwanted mineralization and provide novel therapeutic targets for preventing ectopic calcification in degenerative diseases.



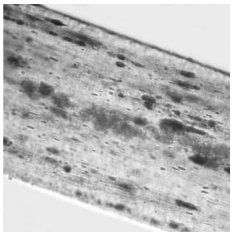
OutFoxing obesity. Hepatocyte nuclear factors-3 (Foxa-1–3) are winged forkhead transcription factors that regulate gene expression in the liver and pancreatic islets and are required for normal metabolism. Markus Stoffel and colleagues show that Foxa-2 is expressed in preadipocytes and induced de novo in adipocytes of genetic and diet-induced rodent models of obesity (pages 345–356). Foxa-2 expression inhibited adipocyte differentiation in vitro and increased expression of genes involved in adipocyte metabolism. Haploinsufficiency in Foxa-2 led to increased adipogenesis in diet-induced obesity and defects in adipocyte glucose metabolism. These data indicate that Foxa-2 mediates a negative feedback mechanism on adipocyte differentiation and a feed-forward mechanism on adipocyte insulin sensitivity. This study uncovers an important and novel pathway for adipocyte homeostasis and points to Foxa-2 as a potential target for novel therapeutic approaches to obesity.



$P2Y_{12}$: a growing role in growing thrombi. A recently identified drug to block platelet aggregation and thrombosis targets the ADP receptor $P2Y_{12}$. However, $P2Y_{12}$ antagonists are utilized clinically at levels that only block half of the $P2Y_{12}$ on platelets and that require aspirin cotherapy for optimal efficacy. Pamela Conley and colleagues now clearly delineate the role of $P2Y_{12}$ in platelet thrombosis with a $P2Y_{12}$ knockout mouse (pages 398–406). In an in vivo artery injury model, the appearance of thrombi was delayed in the $P2Y_{12}$ null mice; when they did appear, the thrombi were highly unstable and never reached occlusive size, even in the absence of aspirin. $P2Y_{12}$ was found to be a critical player in platelet adhesion and activation and in thrombus growth and stability. These findings have important implications for the potential of $P2Y_{12}$ antagonists as well as for the continued development of this class of drugs.



IL-10 responsible for tolerance to allergens. The development and mechanisms of tolerance to allergens are poorly understood. Specific tolerance to contact allergens can be established by repeated exposure to the allergen in low doses. Marcus Maurer and colleagues now show that this only works in the presence of IL-10, as IL-10–deficient mice failed to develop low zone tolerance (LZT) unless the animals were reconstituted with IL-10 during LZT induction (pages 432–439). Two distinct populations of lymph node regulatory T cells were found to be the source and target cells of IL-10. LZT in normal mice was also greatly enhanced by IL-10. These findings suggest that a clearer understanding of the role of IL-10 in tolerance induction may lead to strategies to prevent allergies and other harmful immune responses.



A new form of Griscelli syndrome. Griscelli syndrome (GS) is a rare autosomal recessive disorder, with patients presenting partial albinism and either a primary neurological impairment or a severe deficit in immune function. Two different genetic forms, GS1 and GS2, account for the mutually exclusive neurological and immunological phenotypes. Mutations in the gene encoding the molecular motor protein Myosin5A cause GS1, whereas mutations in the gene encoding the small GTPase Rab27a are responsible for GS2. Geneviève de Saint Basile and colleagues now present genetic and functional evidence that a third form of GS, restricted to the characteristic partial albinism expression of this syndrome, results from mutation in the gene that encodes melanophilin (pages 450–456). This spectrum of GS conditions pinpoints the distinct molecular pathways used by melanocytes, neurons, and immune cells in secretory granule exocytosis.