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In This Issue

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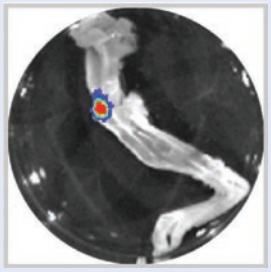
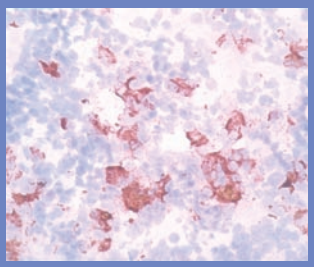
KLF6-SV1 helps prostate cancer spread its wings Metastatic prostate cancer (PCa) is the second most common cause of death from cancer for men. Defining the molecular mechanisms by which localized PCa progresses to metastatic PCa and the markers of this transition is important for developing strategies to identify individuals at risk of metastatic disease. Kruppel-like factor 6 (KLF6) is a tumor suppressor gene, but Narla, DiFeo, and colleagues have now shown that the KLF6 splice variant KLF6-SV1 is expressed at higher levels in prostate tissue from individuals with metastatic PCa than in prostate tissue from individuals with localized PCa (pages 2711–2721). Further analysis indicated that increased expression of KLF6-SV1 in men with localized PCa predicted decreased survival and more rapid disease recurrence. Consistent with increased levels of KLF6-SV1 having a biological role in metastasis, a PCa cell line overexpressing KLF6-SV1 metastasized more rapidly and more often than the parent PCa cell line when assessed in a mouse model of metastatic PCa. Conversely, siRNA knockdown of KLF6-SV1 expression in established tumors in a mouse model of PCa reduced tumor growth. These data led the authors to suggest that KLF6-SV1 might provide a therapeutic target for PCa as well as being a good indicator of whether a localized PCa tumor will progress to metastatic disease. Calpain inhibitors never forget Calpains are calcium-activated […]

KLF6-SV1 helps prostate cancer spread its wings



Metastatic prostate cancer (PCa) is the second most common cause of death from cancer for men. Defining the molecular mechanisms by which localized PCa progresses to metastatic PCa and the markers of this transition is important for developing strategies to identify individuals at risk of metastatic disease. Kruppel-like factor 6 (*KLF6*) is a tumor suppressor gene, but Narla, DiFeo, and colleagues have now shown that the *KLF6* splice variant *KLF6-SV1* is expressed at higher levels in prostate tissue from individuals with metastatic PCa than in prostate tissue from individuals with localized PCa (pages 2711–2721). Further analysis indicated that increased expression of *KLF6-SV1* in men with localized PCa predicted decreased survival and more rapid disease recurrence. Consistent with increased levels of KLF6-SV1 having a biological role in metastasis, a PCa cell line overexpressing KLF6-SV1 metastasized more rapidly and more often than the parent PCa cell line when assessed in a mouse model of metastatic PCa. Conversely, siRNA knockdown of *KLF6-SV1* expression in established tumors in a mouse model of PCa reduced tumor growth. These data led the authors to suggest that KLF6-SV1 might provide a therapeutic target for PCa as well as being a good indicator of whether a localized PCa tumor will progress to metastatic disease.

Host-derived lipids: a link between leprosy and atherosclerosis?



The intracellular pathogen *Mycobacterium leprae*, which is the causative agent of leprosy, survives by both evading the host immune system and using host-derived lipids to promote its growth and virulence. A link between these two factors influencing *M. leprae* survival in the lesions of individuals with the lepromatous form of human leprosy (L-lep) has now been uncovered by Cruz and colleagues (pages 2917–2928). Host genes encoding proteins involved in lipid metabolism (for example, several phospholipases) were found to be upregulated in human L-lep lesions. Consistent with this, the lipid-laden macrophages in human L-lep lesions that are known to harbor *M. leprae* were found to also accumulate host-derived oxidized phospholipids. Further in vitro analysis indicated that some of these host-derived oxidized phospholipids inhibited innate immune responses and that this inhibition was abrogated by HDL, a scavenger of oxidized phospholipids. The accumulation of macrophages laden with host-derived oxidized phospholipids in L-lep lesions is strikingly similar to what is observed in atherosclerotic lesions, leading the authors to implicate the link between host lipid metabolism and innate immunity in the pathogenesis of both microbial infection and metabolic disease.

Bringing stability to the protein deficient in phenylketonuria

Phenylketonuria (PKU) is an inherited disease caused by mutations in the gene encoding phenylalanine hydroxylase (PAH), an enzyme that catalyzes the hydroxylation of L-Phe to L-Tyr. Most PKU-causing *PAH* mutations lead to protein misfolding and increased turnover. So, Pey and colleagues have suggested that using pharmacological chaperones to stabilize the mutant forms of PAH found in individuals with PKU (PKU mutants) might provide an alternative to the current treatment for PKU, which for many years was simply to restrict the amount of L-Phe in the diet, although supplementation with the cofactor tetrahydrobiopterin has recently been shown to be beneficial (pages 2858–2867). Four chemicals that increased the thermal stability of wild-type PAH but did not inhibit its function were identified by high-throughput screening. Two of these chemicals were analyzed in more detail and found to stabilize the functional tetrameric conformation of both wild-type PAH and PKU mutants. These compounds also increased the activity and amount of both wild-type PAH and PKU mutants in human cell lines engineered to express these proteins. Further, mice orally administered low doses of these compounds for 12 days showed increased PAH activity in the liver. The authors hope that future studies optimizing the stabilizing effects will lead to the identification of more potent pharmacological chaperones.

Calpain inhibitors never forget

Calpains are calcium-activated cysteine proteases involved in memory formation, and their overactivation has been linked to the pathogenesis of Alzheimer disease (AD). Using both a broad-spectrum cysteine protease inhibitor and a highly specific calpain inhibitor, Trinchese and colleagues have shown that calpain inhibition improves spatial-working memory and associative fear memory in the APP/PS1 mouse model of AD (pages 2796–2807). It is thought that synaptic dysfunction contributes to the impaired cognitive function in individuals with AD. The ability of calpain inhibitors to improve cognition in the APP/PS1 mouse model of AD was likely a result, at least in part, of restoration of normal synaptic function, as was observed in cultured dissociated hippocampal cells and hippocampal slices from APP/PS1 mice exposed to calpain inhibitors. At a molecular level, the calpain inhibitors were found to restore to normal both levels of phosphorylation of cAMP regulatory element–binding protein (CREB) and localization of the synaptic protein synapsin I. The authors therefore suggest that inhibiting calpains might prove beneficial to individuals with AD, improving their memory.