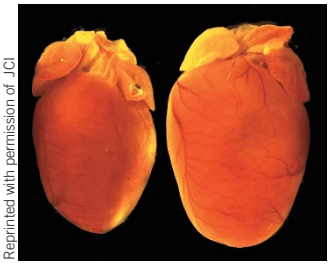
## Histones of the heart



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Cardiac hypertrophy, the enlargement of the heart in response to stresses like high blood pressure, is a main cause of congestive heart failure. In the September *Journal of Clinical Investigation*, Hyun Kook *et al.* show that a regulator of cardiac hypertrophy modulates cardiac growth and proliferation through histone deacetylase (HDAC). The results open the door to the possibility of treating heart failure with HDAC inhibitors, already in phase 1 and 2 clinical trials for cancer.

Kook *et al.* found that mice overexpressing Hop, a regulator of cardiac hypertrophy, had enlarged hearts (right) compared with wild type (left). The investigators provide evidence that Hop regulates transcription as part of a protein complex containing a member of the class I HDAC family.

This complex, it seems, regulates transcriptional events that promote hypertrophy. In support of this notion, the investigators found that administration of an HDAC inhibitor prevented hypertrophy in the Hop-overexpressing mice. The same inhibitor also counteracted hypertrophy in a chemically induced model of the disease. In contrast, earlier studies had found that a class II HDAC appeared to negatively regulate hypertrophy. The new data suggest that the role of HDACs in cardiac hypertrophy may not be quite so simple.

## Suffocation and cell migration

A tumor suppressor that acts through a central regulator of the cellular response to hypoxia is now implicated in metastasis. In the 18 September *Nature*, Peter Staller *et al.* document how inactivation of the von-Hippel Lindau (VHL) tumor suppressor protein sets into motion a series of events that promote migration of cancer cells to sites distant from the tumor.

VHL is inactivated in many kidney tumors and several other tumor types. Among other cellular tasks, VHL targets a subunit of hypoxia-inducible factor (HIF) for destruction in the presence of oxygen. Inactivation of VHL upregulates HIF expression. The investigators report that HIF, in turn, influences the expression of the chemokine receptor CXCR4, a protein that promotes metastasis.

CXCR4 binds chemokines—secreted proteins that allow migrating cells to navigate to specific organs. Studies of breast cancer cells have also found that tumor cells expressing CXCR4 can migrate to chemokine-expressing organs distant from the tumor. But how tumor cells become programmed to express CXCR4 has been unclear.

The investigators report that CXCR4 was consistently overexpressed in tumors lacking VHL. Moreover, CXCR4 expression could be induced either by transfecting VHL into tumor cells or by starving the cells of oxygen. CXCR4 expression was not associated with tumor stage or differentiation grade in an analysis of a battery of human tumors, but it was strongly associated with poor survival.

The investigators propose that inactivation of VHL early in tumorigenesis promotes the expression of CXCR4 and could predispose tumors to metastasis. They also note that hypoxic conditions, present in many tumors, might also induce CXCR4 expression and promote migration of cancer cells to distant sites.

Written by Charlotte Schubert

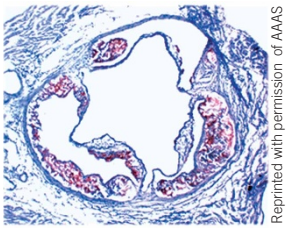
## Presenilin's new task

New work reveals the inner workings of presenilin, a molecule implicated in Alzheimer disease. In the September 4 *Cell*, Philippe Marambaud *et al.* report that presenilin regulates proteins known to mediate the formation of memories.

Previous work had shown that presenilin promotes the cleavage of the amyloid precursor protein, creating the amyloid-β peptide that accumulates in the brains of patients with Alzheimer disease. But presenilin has several substrates. The investigators found that presenilin also promotes the cleavage of the neuronal molecule N-cadherin, which mediates events such as axonal outgrowth. The investigators find that the N-cadherin cleavage product promotes the degradation of the transcription factor CREB-binding protein (CBP). CBP and its partner CREB mediate neuronal development, survival and synaptic function, and they have a crucial role in memory formation.

The investigators went on to look at mutations in presenilin associated with familial Alzheimer disease. Proteins encoded by mutant presenilin genes were unable to cleave N-cadherin and did not interfere with CBP/CREB. CBP interacts with a number of other transcriptional regulators, so presenilin's influence on CBP might extend beyond CREB.

## Softening the arteries



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**Inactivation of a receptor in macrophages substantially reduces atherosclerotic lesions in a mouse model, according to a report in the 11 September *Science*. Lipid-accumulating macrophages, or foam cells, are the major component of artery-clogging lesions. Lipid transport in these macrophages requires a member of the peroxisome proliferator–activated receptor (PPAR) nuclear receptor family, PPAR-γ. Chih-Hao Lee *et al.* investigated another receptor in the family, PPAR-δ. Deletion of PPAR-δ from foam cells reduced atherosclerotic lesions in their model by more than 50% compared with wild type. The investigators found that PPAR-δ does not modulate cholesterol movement through the cell. Instead, PPAR-δ seems to regulate the release of proinflammatory molecules.**

## Prescription for pain

A compound that activates a cannabinoid receptor can counteract neuropathic pain in mouse models, report Mohab Ibrahim *et al.* in the September 2 *PNAS*. Neuropathic pain, such as painful hypersensitivity to touch or heat, plagues about 1% of the human population. Many patients respond poorly to drug treatment and often experience side effects. Most prescribed drugs affect the central nervous system, as well as the peripheral nervous system, which mediates neuropathic pain. The investigators aimed to bypass such side effects by targeting the $CB_2$ cannabinoid receptor, which does not seem to be expressed in the central nervous system. They found that the selective $CB_2$ agonist AM1241 reversed symptoms of hypersensitivity to touch and heat in mice, without apparent ill effects. Exactly how AM1241 works is unclear. But $CB_2$ is expressed mainly on mast and immune cells, which are known to release mediators that sensitize primary afferent neurons involved in neuropathic pain. Among other possibilities, say the authors, AM1241 could interfere with this sensitization process.