is important, however, to determine whether ABC1 is regulated entirely at the mRNA level or whether its activity might also be regulated by posttranslational modifications, or allosterically, through interaction with specific lipids within the membrane.

### Implications for plasma lipid metabolism

The discovery of ABC1 has substantial implications for plasma lipoprotein metabolism. ABC1 seems to play an obligatory step in HDL metabolism, transforming lipid-poor apo-AI particles into nascent HDL particles that can interact with the apo-B-containing lipoproteins (for example, low-density lipoproteins) and function in other metabolic processes (panel *a* of figure). Whether the 'activation' of lipid-poor apo-AI particles involves a direct interaction between ABC1 and apo-AI is unknown and requires investigation. In the absence of ABC1 (panel *b* of figure), lipid-poor apo-AI particles do not acquire cellular lipids and are therefore cleared rapidly from the plasma[5]. Because the lipid-poor apo-AI particles are not transformed into nascent HDL particles, HDL metabolism never gets off the starting block, and its metabolism is effectively dissociated from that of the apo-B-containing lipoproteins. The low LDL cholesterol levels in the plasma of people with Tangier disease and the triglyceride enrichment of 'Tangier' LDL are almost certainly consequences of this dissociation.

Other inherited metabolic defects, such as the loss of ability to generate apo-B-containing lipoproteins[14–16], or loss of ability to transfer polar lipids from very low-density lipoprotein to HDL (ref. 17), seriously perturb HDL metabolism. But respectable levels of HDL (20–50% of normal) still exist in those conditions. That this is not the case in Tangier disease indicates that cell-derived lipids are essential for the production of metabolically competent HDL. Why free cholesterol and phospholipids from the apo-B-containing lipoproteins are apparently incapable of substituting for cellular lipids is perplexing and requires additional investigation.

Heterozygotes for ABC1 deficiency have half-normal levels of HDL cholesterol. This was suggested earlier by investigations of the families of people with Tangier disease[5]. In addition, the current study by Michael Hayden and colleagues[2] demonstrates that familial hypoalphalipoproteinaemia (characterized by low HDL cholesterol levels but no overt cholesterol ester accumulation in tissues) can be caused by heterozygous mutation of *ABC1*.

It will be interesting to determine whether subtle polymorphisms in *ABC1* contribute to the 10–20% reduction in HDL levels that are so commonly observed in people with atherosclerotic coronary heart disease. In addition, it will be of interest to determine whether *ABC1* overexpression in transgenic animals increases HDL cholesterol levels and reduces the accumulation of cholesterol ester-rich macrophages in atherosclerotic plaques. Such a phenotype would obviously make upregulation of *ABC1* an attractive goal for the pharmaceutical industry—but predicting the consequences of *ABC1* overexpression is not easy, as it might perturb plasma-membrane lipids and adversely affect cell viability.

The identification of *ABC1* has posed new questions for the future of the lipid and lipoprotein field. But what of Tangier Island, the sand bar where this story began? Unfortunately, its shores are eroding. Without sea walls and beach replenishment, the island could simply disappear within the next century. Given its rich history, such a fate would be unmerciful and sad. It would also be ironic, as the disease that bears the island's name has provided a solid footing and bright future for those seeking to understand HDL and cholesterol efflux from cells. □


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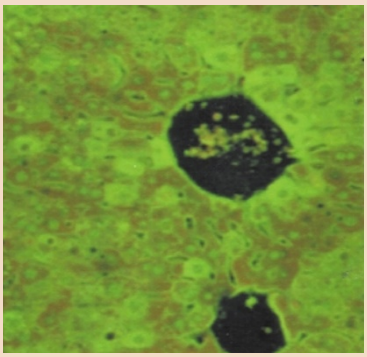
## Having a go at the hepatitis B virus

The hepatitis B virus (HBV) is a canny one. Acute infection is usually cleared by the immune system. But in some cases, chronic infection sets in, accompanied by integration of the virus into the nuclear DNA of liver cells. To make matters worse, HBV carriers (of which there are about 350m) have a high risk of developing chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Research into how HBV infection translates into HCC and CLD has been stymied by the lack of suitable animal models: only woodchucks, ducks and squirrels are naturally infected with related HBV-like viruses. Mark Feitelson and colleagues now describe a promising animal model in this month's issue of *Nature Medicine* (vol. 5, 907–912; 1999). They engineered transgenic expression of the virus in mice with severe combined immunodeficiency. The resultant mice support HBV gene expression and replication in the liver and elsewhere (see picture for hepatocyte expression of an HBV antigen); infusing them with unprimed, syngeneic splenocytes partially clears virus from the serum and liver. Notably, the mice sustain persistent virus replication and develop CLD, but, so far, not HCC. Molecular dissection of these



mice should help to identify the virus antigens and corresponding immune responses that contribute to CLD.

—*Bette Phimister*