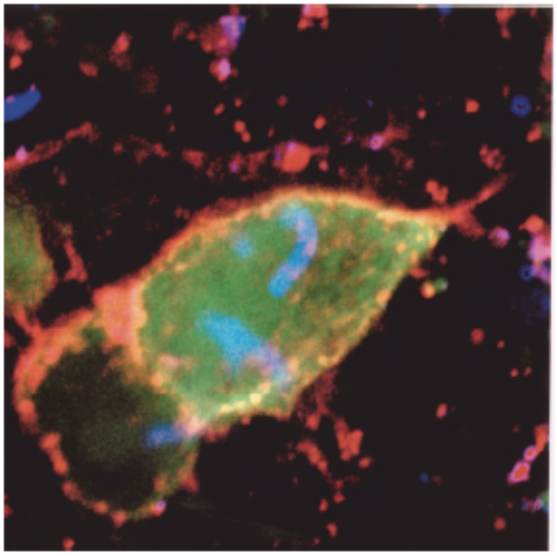
Picky *Plasmodium* search for the perfect host

Although most parasites invade host cells by forming an internalization vacuole that carries them into the cell without disrupting the plasma membrane, *Plasmodium* spp. sporozoites have found a way to enter cells by a completely novel mechanism. The sporozoite, the infective stage of the malaria parasite, is transmitted by bite of infected Anopheles mosquitoes. In humans, sporozoites migrate from the skin to liver cell, where they enter hepatocytes and mature into the merozoites that enter the bloodstream and infect red blood cells. Little is known about the cell biology of the sporozoite, including the mechanisms they use to enter and exit cells.

Videos made years ago by Jerome Vanderberg at the New York University School of Medicine showed sporozoites that appeared to enter and exit cells without the aide of an internalization vesicle, but this behavior was originally believed to be an artifact. Upon re-examining the old videos, NYU cell biologists became intrigued by the phenomenon and decided to investigate further. "At the time people believed that the parasites were going underneath the cells, but when we saw these movies, we really had the impression that the sporozoites were moving through them," said NYU researcher Ana Rodriguez.

Rodriguez and colleagues began using time-lapse video analysis and fluorescent antibody labeling experiments to track the movement of *Plasmodium* sporozoites in cell cultures. In the 5 January issue of *Science*, Mota *et al.* (*Science* **291**, 141–144) demonstrate that the parasites are actually capable of breaching the plasma membrane to enter and exit cells. The confocal image (picture) shows two sporozoites (blue) that have disrupted the hepatocyte plasma membrane (red) and are able to move throughout the cytosol (green), independent of vacuolar membranes. In some cases the cell is capable of rapidly resealing the broken membrane, but in other cases the breakage causes cytoplasmic leakage and cell death. Mota *et al.* determined that sporozoites transverse an average of four cells an hour, and suggest that they may need to traverse several cells in search of hepatocytes that are suitable for infection.



This is the first demonstration that a non-viral pathogen can transverse the cell membrane without forming an internalization vacuole. The authors plan to uncover the exact mechanism used by the parasites to enter the cell. "The process may be mediated by proteases or lipases that the sporozoite releases to destroy the plasma membrane, or else by the mechanical force of the parasite itself," said Rodriguez, the senior author on the study. "Perhaps one day we may learn how to inhibit this process, and then malarial infection could be abrogated at its first step."

Kristine Novak

Hereditary prostate cancer: a new piece of the puzzle

An eagerly awaited prostate cancer susceptibility gene has been announced. But does the candidate live up to expectations?

ÅKE BORG

Prostate cancer is the most common malignancy in North American and European men, and represents a major public health challenge. Traditionally considered a disease of elderly men, a considerable proportion of cases occur in men in their pre-retirement years. New means of identifying individuals at risk and strategies for early detection and preventive care are greatly needed.

Prostate cancer has, like other common cancers, a recognized familial component[1]. Though major susceptibility genes for colorectal and breast cancer have been identified and characterized, the genetic factors that underlie inherited prostate cancer remain elusive. Several research groups have done extensive work to identify these factors, performing genome-wide scans on large sets of families to search for genetic linkages. A number of putative loci have been identified (Fig. 1). These include *HPC1*, *PCAP*, *HPCX* and *CAPB*. However, confirmatory linkage studies are generally lacking, and a strong candidate gene has not yet been cloned.

The hereditary form of prostate cancer is remarkably heterogeneous. This adds to the other obstacles of linkage detection, which include a high rate of sporadic cases, late age of diagnosis, various modes of inheritance (autosomal, X-linked/dominant or recessive), and strong influences from modifying factors. In the February issue of *Nature Genetics*, Tavtigian *et al.*[2] identify a candidate prostate cancer susceptibility gene; they report a significant linkage in high risk prostate cancer families to markers on chromosome 17p (two point logarithm of odds (LOD) score of 4.5 for D17S1289, meaning that there is less than a 1 in 10,000 chance of random association). Moreover, the authors provide evidence of germline frameshift and nonconservative missense mutations, as well as disease-associated common variants, in a candidate gene named *ELAC2* (Fig. 1).

Homologues to *ELAC2* have been described in yeast, bacteria and plants[2] (www.ncbi.nml.nih.gov). These genes are predicted to encode a highly conserved metal-dependent hy-