ning to emerge, whereby BRCA2 sequesters Rad51 protein in an inactive state from which it can be activated in response to DNA damage. The correlation with disease-associated mutations in the BRC repeats is provocative, and the structures invite new models regarding BRAC2 function. The structural determination of the Rad51- and ssDNA-interacting domains from the mammalian BRCA2 protein is providing unprecedented insight.

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picture story

Sabotage through structural mimicry

If a virus is to prosper inside a living host, it needs to be able to neutralize the immune response that the host organism mounts against foreign invaders. It turns out that mammalian DNA viruses have developed a range of ingenious strategies to evade immune responses that are mediated by chemokines, a group of ~50 proteins present in the mammalian circulatory system that activate adaptive immunity and control leukocyte migration. For example, their viral genomes may encode specialized G-protein coupled receptors (the targets of chemokine function) or specify the production of proteins that stimulate or antagonize the host's chemokine receptors. In essence, viruses encoding their own set of ligands and receptors can manipulate cellular signaling at will. If this alone would not suffice, yet other viruses show that an alternate strategy is to bind endogenous chemokines and thereby throw a cloak of confusion over the immune response. But how can a viral protein hijack an entire chemokine response pathway?

In a recent paper, Alexander *et al.* (*Cell* **111**, 343–356; 2002) report the crystal structures of a chemokine scavenger with broad chemokine specificity from the murine γherpesvirus68 (γHV68) and its complex with the CC class chemokine MCP-1. M3, as the 42 kDa scavenger protein is known, appears to bind a wide range of murine and human chemokines, and is required *in vivo* both for virulence and for inflammatory responses in the host. The structure of the M3–MCP-1 complex reveals a 2:2 complex formed by

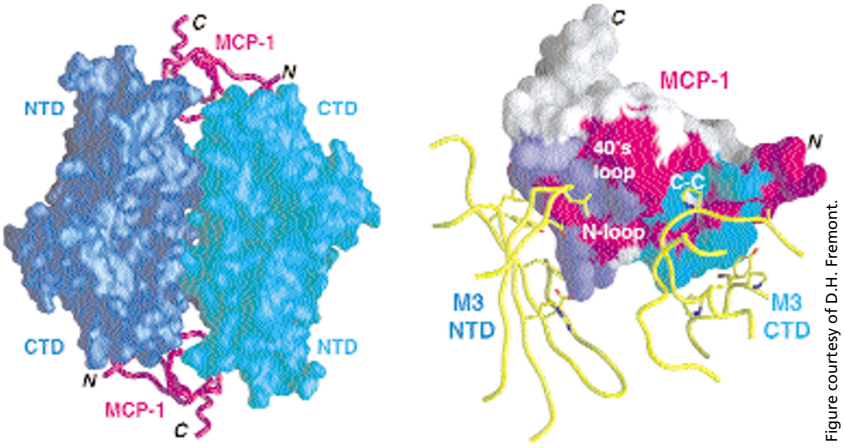

Figure courtesy of D.H. Fremont.

a M3 dimer and two independently associating MCP-1 chemokines (left, molecular surface of M3 is shown in blue and cyan). MCP-1 is recognized by the N-terminal and C-terminal domains of M3 (NTD and CTD, respectively). The NTD recognizes residues in the so-called chemokine 'N-loop' and '40's loop' of MCP-1, whereas the CTD binds the N-terminal region including the CC disulfide bond (right, molecular surface of MCP-1; M3-interacting residues shown in blue and cyan). The ability of M3 to bind a broad range of chemokines with significant but differing affinities seems to stem from structural features of the M3 protein: the use of adaptive, flexible loops as primary binding determinants, a dimeric architecture of the binding site and, perhaps, a very high electrostatic complementarity between the molecular surfaces of M3 and many of its chemokine substrates, exemplified by MCP-1.

The M3–MCP-1 structure also reveals that the herpesvirus M3 protein sequesters chemokines through structural mimicry. The MCP-1 residues bound by M3 are identical to those that are required for MCP-1 interaction with its endogenous CCR2 G-protein coupled receptor, even though there is no sequence homology between M3 and CCR2. The M3 protein thus mimics CCR2 and, by doing so, can lure MCP-1 into binding the viral bait. This viral chicanery severely compromises the host's immune system by removing a necessary chemokine ligand from circulation. The structure by Alexander *et al.* thus reveals how herpesvirus has come up with its own solution to fooling chemokines and their receptors.

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