Kaposi’s sarcoma-associated herpesvirus (KSHV) has evolved a novel means of evading the human immune system: two KSHV proteins, MIR1 and MIR2, cause immune recognition molecules on the host cell surface to be internalized and degraded in the endosome. But how do MIR1 and MIR2 accomplish this? On page 1265, Coscoy et al. present the surprising finding that the viral proteins ubiquitinate their cellular targets, and that this modification causes the immune recognition molecules MHC-I, B7.2, and ICAM-1 to be endocytosed. In addition to uncovering a new use for ubiquitination, the work identifies the first of a new class of ubiquitin ligases.

The authors found that the ubiquitination requires the PHD subfamily zinc finger motifs found in the MIR1 and MIR2 membrane-bound viral proteins. In vitro analysis of MIR2 shows that it is an E3 ubiquitin ligase, making it the first such enzyme found to use a PHD subfamily rather than a RING subfamily zinc finger. MIR1 and MIR2 may interact with immune recognition molecules on the cell surface and ubiquitinate lysine residues in the cytoplasmic domains of the host proteins.

The substrates of MIR1 and MIR2 are targeted to the endosome rather than the proteosome, so the results add immune recognition molecules to the growing list of proteins whose endocytosis can be regulated by ubiquitination. The two viral proteins were originally identified in a screen for inhibitors of immune recognition, so Coscoy et al. are now searching for additional substrates that might be ubiquitinated by MIR2.

Another group, studying a MIR1 homologue called MK3 in a murine herpesvirus, has independently determined that MK3 causes the ubiquitination and degradation of mouse MHC-I (Boname, J.M., et al. 2001. Immunity. 15:627–636). In contrast to the situation in KSHV infection, though, MK3-driven ubiquitination targets MHC-I to the proteosome.

**Motoring through the checkpoint**

The mitotic spindle checkpoint is a crucial cellular safety feature ensuring that both daughter cells will receive the correct number of chromosomes during cell division. Somehow the checkpoint is turned off only when the chromosomes are attached and aligned. Now on page 1159, Howell et al. show that a transport system using the cytoplasmic dynein/dynactin microtubule motor depletes several proteins from the outer domain of the kinetochore to inactivate the spindle checkpoint and allow mitosis to proceed.

Previously, Howell et al. found that the Mad2 checkpoint protein is transported from kinetochores to the spindle poles along spindle microtubules. The authors have now found that the microtubule motors CENP-E and cytoplasmic dynein, as well as the checkpoint-related proteins BubR1 and the 3F3/2 antigen, are also depleted from kinetochores and accumulate at the spindle poles. Inhibiting dynein/dynactin activity stops this transport process and simultaneously blocks mitosis at metaphase.

The data suggest that proteins in the outer kinetochore domain maintain a dynamic equilibrium that shifts as the kinetochore interacts with microtubules. Once the association pathways are blocked, constitutive dissociation pathways, including dynein/dynactin transport, deplete proteins from the metaphase kinetochores and inactivate the checkpoint. Recent results in *Drosophila melanogaster*, in which mutations in cytoplasmic dynein cause checkpoint-related proteins to accumulate at metaphase kinetochores, underscore the importance of dynein in kinetochore disassembly (Wojcik, E., et al. 2001. Nat. Cell Biol. 3:1001–1007).
Self-stimulation feels different

On page 1123, Maheshwari et al. show that the way a growth factor is delivered to a cell can profoundly affect the cell’s response. The work supports a new model for mammary epithelial cell migration in response to EGF stimulation, and suggests that growth factor-based therapies may be destined to fail if they are not presented to cells correctly.

The authors previously developed an experimental system in which mammary epithelial cells expressing the EGFR (EGFR) can be stimulated by EGF through autocrine, paracrine, or intracrine mechanisms. In the new work, autocrine stimulation, in which EGF is secreted from the cells to bind its receptor on the cell surface, causes the cells to migrate rapidly with persistent direction. But adding EGF protein exogenously for paracrine stimulation, or expressing a processed form of the growth factor to bind to the EGFR pool inside the cell (intracrine stimulation) both cause a “scattering” response in which the cells lack directional persistence.

The results suggest that autocrine stimulation provides directionality, possibly by localized formation of EGF–EGFR signaling complexes on the cell surface. It also seems that biotechnologists hoping to exploit growth factors for tasks ranging from tissue engineering to cancer therapy may need to work on their delivery.

Turning back an invasion

The ability of tumor cells to migrate through the body and invade new tissues is a major focus for research that could lead to new cancer therapies. On page 1345, Uekita et al. demonstrate that the membrane-bound matrix metalloproteinase MT1-MMP, which functions in both migration and invasion, must be recycled continuously from the cell surface to sustain both processes. Blocking the recycling process inhibits the invasive phenotype.

Previous work had shown that MT1-MMP localizes at the migration edge, but it remained unclear how the enzyme was regulated. The authors show that specific sequences in the cytoplasmic tail of MT1-MMP bind to a component of clathrin-coated pits, and that mutations in these sequences prevent internalization and cause the enzyme to accumulate on the cell surface. Although the internalization-defective enzyme specifically accumulates at the migration edge, it does not promote migration or invasion in various assay systems, indicating that the protein must turn over to remain active.

The authors hypothesize that inactivation of MT1-MMP on the cell surface by degradation or inhibitors necessitates continuous replacement of the enzyme; as front-line troops wear out, they are replaced by new recruits. By defining the small motif required for this recycling process, the authors have also identified a potential molecular target for drugs that might inhibit tumor cell metastasis.