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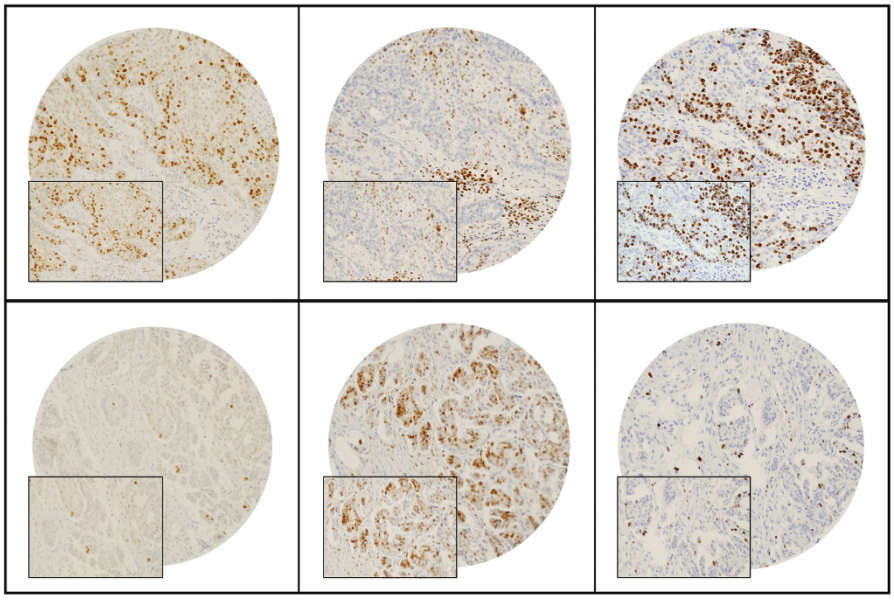

Targeting the proteasome in ovarian carcinoma

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The ubiquitin–proteasome system regulates several important proteins involved in cell-cycle progression and apoptosis through ubiquitin-mediated degradation. Hence, proteasome inhibition has been suggested as a strategy for treating cancer cells. Bortezomib (Velcade; Millennium Pharmaceuticals) is a proteasome inhibitor that has been approved by the US Food and Drug Administration for the treatment of multiple myeloma and mantle cell lymphoma and is in clinical trials in a number of other cancers. One well-known target of bortezomib is S-phase kinase protein 2 (SKP2), a ubiquitin ligase that is a component of cyclin A–CDK2 S-phase kinase, which specifically phosphorylates p27Kip1, targeting it for degradation. p27Kip1 plays an important role in regulating G1 of the cell cycle. Lack of p27Kip1 promotes cellular proliferation.

To understand whether SKP2 and p27Kip1 might be involved in the pathogenesis of epithelial ovarian cancers (EOCs), Uddin *et al* examined a large series of EOCs and discovered an inverse relationship between SKP2 and p27Kip1 in a distinct subset of EOCs. They found that tumors with high SKP2 and low p27Kip1 had a higher proliferative index and hypothesized that targeting SKP2 with bortezomib might result in decreased tumor cell proliferation. They found in a mouse xenograft model both *in vitro* and *in vivo* that bortezomib had a significant effect on proliferation and also induced cell death through the classic apoptosis pathway. They also found that bortezomib synergized with cisplatin. In summary, this important translational study suggests that bortezomib may have a role in the treatment of EOCs, at least in the subset that has high SKP2 and low p27Kip1.

Personalized surveillance of lymphoma

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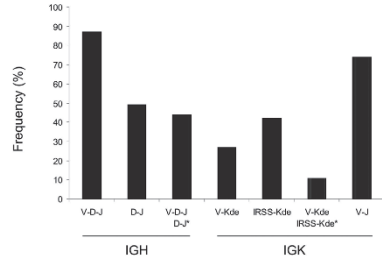
Monitoring disease states during and after cancer therapy has important implications for treatment and prognosis. Although it is theoretically possible to do this for all cancers, it has been put into practice primarily with hematopoietic tumors that have tumor cells and tumor cell products that are accessible in peripheral blood and bone marrow. Burkitt's lymphoma is characterized by t(8;14), which is a convenient target for detecting circulating tumor cells by long-distance polymerase chain reaction (PCR). Long-distance PCR for t(8;14) is currently used to monitor minimal residual disease in Burkitt's lymphoma patients. Detection of minimal residual disease is used to stratify patients for treatment and prognostic purposes. However, t(8:14) is detectable in only about 70% of Burkitt's lymphoma patients.

Given the limitations of long-distance PCR for identification of t(8;14), Lovisa and colleagues examined samples from patients with mature B-cell lymphoblastic leukemia and Burkitt's lymphoma for the presence of clonal immunoglobulin kappa light-chain and heavy-chain rearrangements that could be used to monitor minimal residual disease. They identified at least one target with a sensitivity of at least 10^{-4} in 87% of patients that could be monitored by real-time PCR. Therefore, it appears that a combination of long-distance PCR for t(8;14) and real-time PCR for unique immunoglobulin gene



region rearrangements could be used to monitor disease in patients with mature B-cell lymphoblastic leukemia and Burkitt's lymphoma. Prospective studies will be required to determine the validity of this approach.

New hope for multiple sclerosis patients

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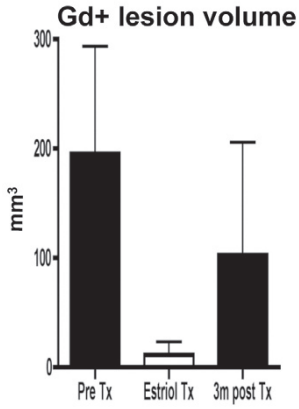
Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) that is thought to have an autoimmune etiology. It is responsible for



considerable morbidity and is notoriously difficult to treat. Matrix metalloproteinase 9 (MMP-9) has been implicated in the pathogenesis of MS because MMP-9 has the ability to disrupt the blood–brain barrier, facilitating the transmigration of T cells and monocytes into the CNS, where they are involved in the destruction of myelin. Interestingly, MS relapses decrease during pregnancy. This has led to the idea that estrogens may confer protection against the disease. Estriol has been shown to lessen disease symptoms in an experimental model of autoimmune encephalomyelitis (EAE), which has been touted as an experimental model of MS. Estriol has been hypothesized to work through downregulation of MMP-9.

Gold and colleagues sought to further investigate the relationship between estriol treatment and MMP-9 *in vivo*. They found that MMP-9 levels were decreased in relapsing–remitting MS patients treated with pregnancy levels of estriol. They also observed decreased levels of MMP-9 in EAE mice treated with estriol. Using selective ER ligands in ovariectomized mice, they showed that the MMP-9-lowering effects of estriol were mediated through estrogen receptor-α. These results are interesting because MMP-9 elevation could represent a common mechanism that facilitates immune-cell attack in a variety of autoimmune diseases. Thus, estriol may find a variety of uses in the treatment of autoimmune disease.

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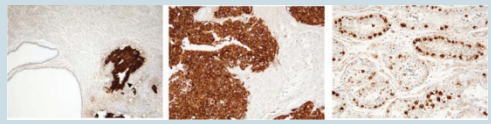
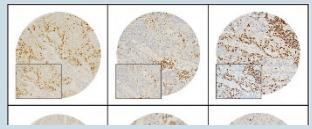


microRNAs in germ-cell development Primordial germ cells (PGCs) are rare and difficult to study. To overcome these limitations, West *et al* have developed a system of differentiating embryonic stem cells into PGCs *in vitro*. In a recent letter in *Nature*, they describe how they used this system to identify *Lin28* as a regulator of PGC development. Their study shows that *Lin28* functions through negative regulation of let-7 microRNA processing, which allows expression of a well-known regulator of PGC development, *Blimp1* (also called *Pdrm1*). In addition to its role in PGC development, the authors found overexpression of LIN28 in human germ cell tumors, thus implicating it in germ cell tumor development. Many questions remain, such as whether *Lin28* targets other microRNAs and how LIN28 functions mechanistically to promote germ cell tumorigenesis. However, importantly, researchers now have a new tool with which to probe PGC development.

Nature 2009;460: 909–913; doi:10.1038/nature08210

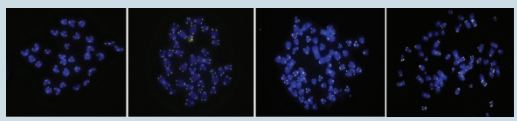
New role for C-CBL in oncogenesis Regions of acquired uniparental disomy (aUPD) arise via mitotic recombination followed by selection for one of the recombination products. They exhibit loss of heterozygosity compared with constitutional DNA without change of copy number. By surveying a variety of myeloid neoplasms for aUPD, Sanada and colleagues identified a 1.4-megabase region of aUPD on 11q that contained the *C-CBL* proto-oncogene. *C-CBL* encodes a protein with E3 ubiquitin ligase activity that is known to downregulate a variety of tyrosine kinases. The authors went on to identify *C-CBL* mutations that correlated strongly with a subset of myeloid neoplasms diagnosed as chronic myelomonocytic leukemia. Finally, they showed that the likely mechanism of action was through loss of C-CBL function, which activated a variety of tyrosine kinases. Thus, unexpectedly, a loss-of-function mutation resulted in a gain-of-function phenotype.

Nature 2009;460: 904–908; doi:10.1038/nature08240



Tank knockout sheds light on functions in immune response TANK (also known as I-TRAF) has been implicated as a positive regulator of nuclear factor-κB (NF-κB) signaling and has been thought to be required for type I interferon signaling. To elucidate the role of Tank *in vivo*, Kawagoe *et al* developed a *Tank* knockout mouse. In a recent article in *Nature Immunology*, they showed that, in contrast to what was expected, Tank acts as a negative regulator of NF-κB signaling and is not involved in type I interferon signaling. They also found that *Tank1*$^{-/-}$ knockout mice developed lethal autoimmune nephritis that appeared to be caused by deposition of immune complexes. It was noted that, because of overlap with lupus nephritis, *Tank1*$^{-/-}$ knockout mice might be a good model of lupus-like immune diseases. Future plans include immune cell–type-specific *Tank* knockouts to elucidate the precise roles of different immune cell types in immune-mediated diseases.

Nature Immunology, advance online publication 9 August 2009; doi:10.1038/ni.1771



Pluripotential stem cells are protected against DNA damage Reprogramming of differentiated somatic cells into pluripotential stem cells known as induced pluripotent stem (iPS) cells has recently become technically feasible, unlocking virtually limitless potential for regenerative therapies for various diseases. However, the process is inefficient. In a recent letter in *Nature*, Marion and co-workers show that p53 presents a barrier to reprogramming, which is exacerbated in the presence of cells with shortened telomeres or damaged DNA. Although p53 may present a barrier to reprogramming, at least it ensures that DNA integrity is maintained. This is of critical importance for using iPS cells for regeneration-based therapies.

Nature, advance online publication 9 August 2009; doi:10.1038/nature08287