cells undergo a metabolic adaptation that may support their growth as well as drug resistance properties.

The researchers then showed that inhibition of the mitochondrial respiratory chain in the resistant population induced cell death. In addition, combining targeting of the mitochondrial respiratory chain with chemotherapy could sensitize the drug's cytotoxic effect in some of the melanoma cell lines studied and reduce tumor growth *in vivo*.

The results support that there is intimate coupling between a tumor cell's proliferative and metabolic states and suggest that compounds that target mitochondrial function currently used in diabetic patients could prevent the development of resistance to cancer therapies. —*VA*

■ AUTOIMMUNITY

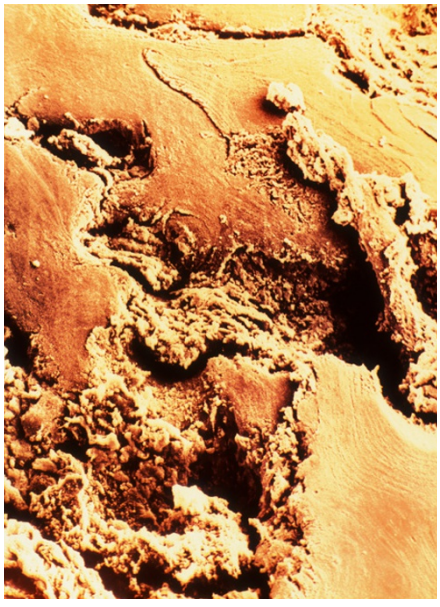
Be more sensitive

Autoantibodies against peptidylarginine deiminases (PADs) may worsen rheumatoid arthritis by increasing the sensitivity of these enzymes for calcium (*Sci. Trans. Med.* **5**, 186ra65).

PADs convert peptidylarginine to citrulline. As citrullinated proteins are effective autoantigens, PADs have been implicated in autoimmune disease. In the case of rheumatoid arthritis, PAD4 is of particular interest, as it is found in synovial fluid. However, PAD4 requires high concentrations of calcium, much higher than those found at the synovium, to work.

Studying samples from patients with rheumatoid arthritis, Erika Darrah *et al.* identified autoantibodies that recognize both PAD3 and PAD4 and that markedly increase the activity of PAD4. By measuring enzyme kinetics, the authors found that the antibodies increased PAD4's sensitivity for calcium by an order of magnitude. People with arthritis with these autoantibodies had worse disease than those who were negative for them.

Although it remains to be seen whether this mechanism is active *in vivo*, the results of this study disclose an intriguing new mechanism for the generation of citrullinated autoantigens and for the pathogenesis of rheumatoid arthritis. —*JCL*



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■ TUMOR SUPPRESSORS

A new PTEN translational variant

Phosphatase and tensin homolog (PTEN) is a key tumor suppressor that it is mutated in multiple cancer types and antagonizes signaling through the phosphoinositide 3-kinase (PI3K) pathway. A recent study identifies a new secreted variant of PTEN that might have therapeutic utility for cancer (*Science* http://dx.doi.org/10.1126/science.1234907).

Benjamin Hopkins *et al.* found an alternative translation start site in the PTEN transcript and showed that this PTEN variant was translated when expressed in cells. Compared with classical PTEN, the alternative PTEN protein (PTEN-Long) had an additional 173 amino acids at its N terminus. The authors detected both forms of PTEN in various human cell lines, including cancer cell lines, but not in those that lacked PTEN. In primary breast tumor tissues, PTEN-Long expression was reduced in the tumors but was higher in the tumor microenvironment than in the tumor or in normal breast tissue.

The researchers then showed that PTEN-Long could be secreted and was present in human plasma and serum. Applied as an exogenous agent, PTEN-Long could block PI3K signaling in cultured cells and was able to regress tumor growth when injected into a number of different mouse xenograft tumor models.

Although further examination of the functions of this alternative PTEN variant is required, the identification of this secreted protein may allow the design of new strategies to restore PTEN to tumor cells. —*MS*

Written by Victoria Aranda, Eva Chmielnicki, Kevin Da Silva, Juan Carlos López and Meera Swami

New from NPG

Vector transmission regulates immune control of *Plasmodium* virulence
Spence, P.J. *et al. Nature* **498**, 228–231 (2013)
The authors show that transmission of the malaria parasite *Plasmodium chabaudi chabaudi* through its mosquito vector modifies the asexual blood-stage parasite, thus altering host immune responses to *Plasmodium* and parasite virulence.

The perivascular niche regulates breast tumour dormancy
Ghajar, C.M. *et al. Nat. Cell. Biol.* http://dx.doi.org/10.1038/ncb2767 (2 June)
This study provides new insights into how disseminated tumor cells are kept dormant by showing that in stable microvessels endothelial-derived thrombospondin-1 (TSP1) maintains breast cancer cells in a quiescent state. In sprouting vessels, TSP1 expression decreases, relieving this suppression and stimulating the growth of metastases.

High-density genotyping study identifies four new susceptibility loci for atopic dermatitis
Ellinghaus, D. *et al. Nat. Genet.* http://dx.doi.org/10.1038/ng.2642 (2 June)
By performing high-density genotyping in thousands of cases and controls, the authors identify four new susceptibility loci for the inflammatory skin disease atopic dermatitis, bringing the total of atopic dermatitis risk loci in European populations to 11.

Nucleation of platelets with blood-borne pathogens on Kupffer cells precedes other innate immunity and contributes to bacterial clearance
Wong, C.H.Y. *et al. Nat. Immunol.* http://dx.doi.org/10.1038/ni.2631 (16 June)
The authors show that platelets collaborate with specialized macrophages called Kupffer cells to clear bacteria. This mechanism occurred before recruitment of other innate immune cells and was needed for survival of the mouse host after bacterial infection.

Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor
Lyst, M.J. *et al. Nat. Neurosci.* http://dx.doi.org/10.1038/nn.343 (16 June)
The authors identify a new mutational cluster in MeCP2, showing that Rett syndrome mutations in this region prevent the interaction of MeCP2 with the co-repressor complex NCoR/SMRT. Mice with a common Rett syndrome mutation in this domain had severe Rett-like phenotypes.